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This document was developed by the Chemical Testing and Assessment Research Committee and it presents a multi-year strategy for ORD's programs on Toxic Substances. This strategy is intended to serve as a basis for preparing each fiscal year's program proposals and for reviewing the progress of ORD's ongoing effort. The document will be updated annually by the Research Committee to refine the strategy and help assure the program's responsiveness to emerging concerns and priorities.

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CHEMICAL TESTING AND ASSESSMENT RESEARCH COMMITTEE - RESEARCH STRATEGY
1979-1985

PREPARED JOINTLY BY:

Office of Research and Development

and

Office of Toxic Substances

U.S. ENVIRONMENTAL PROTECTION AGENCY
Washington, D.C. 20460

PREFACE

The U.S. Environmental Protection Agency relies on thirteen Research Committees to integrate the planning of the bulk of its research programs with the research needs of EPA's regulatory and operational programs. Each Committee addresses a specific portion of the programs managed and implemented by the Agency's Office of Research and Development (ORD). The overall structure of the Committees and corresponding ORD programs are aligned to the organizational structure and function of EPA's regulatory offices: the Office of Pesticides and Toxic Substances; the Office of Air, Noise and Radiation; and the Office of Water and Waste Management. EPA's ten Regional Offices, Office of Enforcement, and Office of Planning and Management are represented on each Committee as well.

Developed by the Chemical Testing and Assessment Research Committee, this particular document presents a multi-year strategy for ORD's programs on Toxic Substances. Like its twelve counterparts, this strategy is intended to serve as a basis for preparing each fiscal year's program proposals and for reviewing the progress of ORD's ongoing effort. The document will be updated annually by the Research Committee to refine the strategy and help assure the program's responsiveness to emerging concerns and priorities.

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AUGUST, 1980

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Chapter One
Executive Summary

SECTION 1

INTRODUCTION

This document was prepared by the Chemical Testing and Assessment Research Committee, established in March, 1979, by the Assistant Administrator for the Office of Research and Development (ORD), U.S. Environmental Protection Agency (EPA). The committee's main function is to address the increased chemical testing and assessment needs resulting from the enactment of the Toxic Substances Control Act of 1976 (TSCA). Included in this responsibility are the establishment of a TSCA research strategy and the provision of aid in developing a TSCA implementation program which provides for quality assurance.

Over the last decade, concern about the impact of toxic substances has resulted in the passage of a broad range of environmental legislation. TSCA was promulgated as "back-up" legislation for these acts. The Clean Air Act (CAA) and the Clean Water Act (CWA) provide for regulation of emission or discharge of toxic substances to air and surface waters. The Marine Protection Research and Sanctuaries Act (MPRSA) controls disposal of toxic substances in the marine environment. Protection of ground waters from toxic insult and control of toxic substances in potable water is mandated by the Safe Drinking Water Act (SDWA). The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) regulates the use of pesticides, and the Resource Conservation and Recovery Act (RCRA) will regulate the land-based disposal of hazardous waste materials. TSCA serves not only to reinforce all of these Acts, but also to fill in the regulatory and data information gaps existing among them.

The Office of Pesticides and Toxic Substances (OPTS), Office of Enforcement (OE), and EPA Regional Offices reflect the Agency's focus on toxic substances control in all of their program implementation activities. This is seen in the ongoing Regional research efforts for air, water, soild waste, water supply, pesticides, and especially toxic substances media, and the OPTS annd OE efforts for TSCA implementation. The Chemical Testing and Assessment Research Committee serves to advise the Assistant Administrator concerning these research efforts.

SECTION 2

TOXIC SUBSTANCES CONTROL ACT - A NEW LAW

The Toxic Substances Control Act is a major environmental statute designed to help eliminate future detriments to the public or environment caused by toxic substances. Several key provisions within TSCA permit EPA to fill the gaps in earlier-promulgated mandates. EPA is currently working to implement all of these provisions.

TSCA is significant in two major areas from the standpoint of toxics control. First, it requires the screening of new chemicals prior to manufacture and distribution in commerce, thereby preventing the introduction of unreasonably hazardous chemicals into the environment. Second, it provides for comprehensive control of existing chemicals shown to pose unreasonable health or environmental risks; control options range in severity from bans on manufacturing or use to strict disposal requirements. However, TSCA control action can only be taken where appropriate protection is not already afforded by other environmental and health-related legislation. To insure that public health and the environment are protected from unreasonable chemical risk, TSCA provides broad information-gathering authority to EPA, including the authority to require testing of chemicals by industry in cases where data are needed to evaluate the risks posed by these compounds.

I. REGULATION UNDER TSCA

Section 4 of TSCA provides EPA authority to require manufacturers and/or processors to test their chemicals for health and environmental effects. This authority is selective, applying only to those chemicals for which the Agency can make certain findings as to the need for testing. A Section 4 testing requirement cannot be applied to all new chemicals. All testing requirements under Section 4 are imposed by rule; each rule specifies not only the chemicals to be tested, but also the nature and standards of the required tests.

The testing provisions of TSCA are designed to support the need of other agencies and to supplement other statutes such as the Occupational Safety and Health Act (OSHA) or the various consumer protection laws. In fact, Section 4(e) establishes an Interagency Testing Committee (ITC) which is to recommend priority chemicals for testing under TSCA.

Section 5 of TSCA establishes a premanufacture notification process for all new chemicals and chemicals proposed for significant new uses (as designated by rule). A new chemical is any chemical not contained in an EPA-compiled inventory of existing chemicals. The manufacturers of these chemicals are required to submit specified information to the Agency at least 90 days prior to production. The Agency has an opportunity to review the submission for 90 days (extendable to not more than 180 days). Unless during this period EPA finds that the chemical poses an unreasonable risk or demonstrates a need for additional testing, the chemical is placed on the inventory without restriction.

Sections 6 and 7 of TSCA provide the control authority for existing chemicals: Section 6 is the general regulatory authority; Section 7 gives the Agency special powers to address imminent hazards. This authority is tempered by Section 9, which requires EPA to determine that regulation under other statutes (e.g. OSHA, CAA, RCRA, or CPSA) is not more appropriate, before TSCA's authority can be invoked. Apart from this limitation, TSCA empowers EPA to limit the production, distribution, disposal, or use of chemicals to prevent unreasonable risks to health or the environment.

The authority to require information reporting is given to EPA in Section 8 of TSCA, and reflects the inadequacy of knowledge about which chemicals are produced, in what amounts, for what purposes, and with what consequences. The information required ranges from the submission of commercial- to exposure- to hazard-related data.

Section 8(a) contains the general reporting authority provided by TSCA. Section 8(b) is the mandate to collect and compile an inventory of chemicals in commerce. Record-keeping and reporting of adverse effects information are covered by Section 8(c). Section 8(d) empowers the Agency to obtain industry and publicly-held health and safety data, and Section 8(e) mandates the submission of information supporting the conclusion that there may be a substantial risk to health or the environment.

As for other TSCA authorities, Section 8 provisions are designed to supplement other statutory mandates and to support the needs of additional programs in carrying out their responsibilities.

The remaining sections of TSCA emphasize the need for coordination of information and research on toxic substances.

II. IMPLEMENTATION OF TSCA

Since the passage of TSCA, preliminary test schemes and assessment approaches have been developed. In the next five years, EPA will revise and expand health and environmental test methods and will develop standards for characterizing chemicals and their fates. Standards for environmental effects testing will likewise be developed.

TSCA testing will most probably follow a tiered approach, beginning with test procedures to determine whether a substance needs further investigation. The main factors considered by ORD in developing a toxic substances research program are: (1) provision of specialized technical assistance to resolve complex problems; (2) development of research capabilities to meet the time frames of TSCA implementation; (3) development of a comprehensive long-range research program to refine continually the test methods and logic assessment schemes; and (4) achievement of continuity and stability in the research program in order to meet future challenges.

SECTION 3

TSCA vs. TOXIC SUBSTANCES

The commercial production of chemicals has followed a trend of steady increase in the U.S., resulting in the present day production of over 40,000 compounds. This increase in production has naturally augmented the presence of toxic substances in the environment and an increase in adverse effects resulting from their use and disposal. To address the wide variety of problems inherent in toxic chemical usage, extensive environmental legislation (as discussed in Section 1) has been promulgated over the past decade. In relation to this legislation, TSCA serves as an "umbrella" mandate, aimed at filling in the research and data information gaps. Unfortunately, in proportion to the pervasiveness of toxic substances in the environment, neither TSCA nor the other promulgated legislation is sufficiently inclusive to solve all or even most of the problems toxic substances present.

In November 1977, the American Chemical Society had a registry of four and one half million distinct chemical substances (not including compounds cited before 1965). Of the 40,000+ compounds currently being produced in the U.S., the manufacture of at least 50 of them exceeds a rate of 1.3 billion lb/yr. Revenue collected from the production and distribution of chemicals amounts to 7% of the U.S. Gross National Product (GNP).

The risks involved with toxic substances must be weighed against the benefits derived in order to achieve a feasible and effective regulatory strategy for toxic substances. As our society continues to become more industry-oriented, chemical production and usage are predicted to increase steadily, especially in the plastics industry. Although increased production introduces more toxics into the environment, it also offers many benefits: new and improved medicines; higher quality consumer goods; better fertilizers for increased food production; etc. The regulation dilemma is often referred to as determining "maximum benefit at acceptable risk."

One of the major obstacles facing EPA regulatory programs is the lack of sufficient data on which to base their regulatory decisions. The production of chemicals has increased so rapidly over such a short period of time that research, in effect, has not had time to "catch up." The adverse environmental and human health effects resulting from the use of most chemicals have yet to even be discovered.

Acute toxic effects have received the most attention to date. Out of necessity, the study of long-term chronic effects, environmental transport and fate, and biological pathways have received less attention, both in terms of funds and time. Moreover, the Agency has in recent years experienced a shortage of laboratory facilities and trained professionals in the areas of toxicology, industrial hygiene, pathology, and other relevant areas.

Perhaps the greatest research need for toxic substances is the development of methods for evaluating the ecological effects and chemical fate of toxics in the environment. If such methods were made available, hazardous chemicals could be identified prior to environmental incidents. Latency periods for diseases caused by exposure to toxic substances may often extend from 20 to 40 years. In the past, such delayed effects have not been identified until well after the chemicals have been introduced into the environment. For example, mercury, nitroso compounds, chloroform, kepone, and the dioxins were manufactured in great quantities until they were discovered to be extremely hazardous to both the environment and humans. Thus, the crux of toxics control is uncovering such deleterious effects from unsuspected substances.

Although the environmental legislation currently in effect and the authority allowed by TSCA for expanded control of industrial production are doing much to solve the toxics dilemma, extensive research is still required to prevent further hazard in the future. In addition, the problems already apparent still require enormous effort to reach any viable solution. This effort will require far more than what the present legislation can offer, both in output of labor and availability of funds.

SECTION 4

CHEMICAL TESTING AND ASSESSMENT RESEARCH COMMITTEE

I. COMMITTEE MEMBERSHIP

The Chemical Testing and Assessment Research Committee (CTARC) is one of thirteen research committees established by ORD under its revised planning process. These committees were formed to explore the effectiveness of joint committee strategy development for regulatory, operational, and research programs. Each committee is responsible for the development of a research strategy for one of the thirteen "research modules" covered under the ORD program: Water Quality; Municipal Wastewater and Spill Prevention; Drinking Water; Industrial Processes; Solid Waste; Mobile Source Air Pollution; Oxidants; Gaseous and Inhalation Particulate Pollutants; Hazardous Air Pollutants; Radiation; Energy; Pesticides; and Chemical Testing and Assessment. As suggested by its name, CTARC is responsible for the Chemical Testing and Assessment module.

The Office of Pesticides and Toxic Substances is the regulatory program office related to the Chemical Testing and Assessment module. Thus, ORD and OPTS work in liaison through CTARC to develop a research strategy. CTARC also works closely with the Office of Enforcement, which works to enforce the implementation program adopted by OPTS.

According to directives set forth by the Assistant Administrator of ORD, CTARC is co-chaired by a senior ORD official and a senior OPTS official. Dr. Michael Waters of ORD and Dr. Warren Muir o OPTS were originally named co-chairmen of CTARC. In April 1980, these positions were assumed by Dr. Vilma Hunt of ORD and Dr. James Reisa of OPTS. The membership of the committee includes representatives from the Office of Enforcement, Office of Pesticides and Toxic Substances, Office of Research and Development, the EPA Regional Offices, and the Office of Planning and Management.

At its organizational meeting in April 1979, CTARC established three subcommittees to plan the research effort for the testing and assessment of chemicals: (1) the health subcommittee; (2) the environmental subcommittee; and (3) the monitoring subcommittee. Each subcommittee is co-chaired by a senior member of ORD and of OPTS.

Until 1980 Dr. Ronald Baron (ORD) and Dr. Jerry Williams (OPTS) served as co-chairmen of the health subcommittee, and Mr. Clinton Hall (ORD) and Dr. James Reisa (OPTS) headed the environmental subcommittee. Currently, Dr. Ronald Baron (ORD) and Dr. C. C. Lee (OPTS) serve as co-chairmen of the health subcommittee, and Dr. William Murray (ORD) and Dr. Michael Heeb (OPTS) head the environmental subcommittee. The monitoring subcommittee is co-chaired by Ms. Phyllis Daly (ORD) and Mr. Martin Halper (OPTS). A new subcommittee on Environmental Engineering and Technology has recently been established and is co-chaired by Mr. Carl Shaffer (ORD) and Dr. Roger Garrett (OPTS).

In addition, ORD's program on Stratospheric Modification Impact Research has been incorporated into CTARC's area of concern. The program addresses the effects on health and ecosystems of increased exposure to ultraviolet radiation due to ozone depletion in the stratosphere. Although the addition of this program to CTARC's purview is too recent to include the program in the present document, it will be included in the next updating of the strategy in early 1981. In the interim, the reader may obtain a specific description of the research and its findings from the annual report to Congress, "Results of Research Related to Stratospheric Ozone Protection."

II. COMMITTEE CHARTER

The CTARC charter, as set forth by ORD, charges the committee with five major tasks:

- Review the current program to familiarize all members with the status of ongoing work.
- Review the upcoming year's plans and formulate appropriate recommendations to improve those plans.
- Participate in the development of budget year plans.
- Develop a multi-year research strategy with sufficient detail for use as a primary planning document in subsequent years.
- Review the quality of ongoing and recently completed research.

The committee works within the framework of the EPA and Federal Planning and budgeting cycles to aid in making responsible resources allocations. The mechanism by which the committee operates is within the annual Zero

Base Budgeting (ZBB) process. CTARC reviews all Decision Units (DU's) relevant to its research module, ranking them in importance and suggesting alterations. ORD considers these recommendations in their final budget decision-making process.

A major output of the committee is the present research strategy document which expresses the committee's view of the kinds of research needed to support a given regulatory strategy area and the general approach which should be taken. The strategy is related to EPA's overall planning process in two ways, through the _Research Outlook_, and through impact on the budget process.

The _Research Outlook_, an annual publication describing EPA's plans for research over a four to five year period, consolidates and describes the strategic aspects of the plans developed by the research committee. At the same time, it builds on the findings of ORD's Strategic Analysis Group on emerging environmental trends, pertinent results from the Exploratory Research Program, and the insights of senior ORD personnel (both at Headquarters and the laboratories). Information contained in the strategy, coupled with specific scientific results that become available, serve as building blocks for the _Research Outlook_.

The second interface between the research strategies and ORD's planning process concerns the document's relationship to budget year planning. The strategies provide major direction for the annual preparation of ORD's Decision Units. These documents describe the annual program proposals which enter the ZBB process and form the basis for both EPA's yearly budget submission to Congress and eventually the program operating plan.

CTARC also serves to assure quality for ongoing and recently completed research. Quality assurance (QA) and quality control (QC) are the joint responsibility of the regulatory (OPTS) and the research (ORD) contingents of the committee.

Chapter Two
TSCA and the Program and Regional Office Strategies

SECTION 1

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES STRATEGY

I. OPTS ORGANIZATION AND FUNCTION RELATED TO TSCA

To implement the many facets of TSCA, three offices have been established within the Office of Pesticides and Toxic Substances (OPTS).

The Office of Program Integration and Information (OPII) was established to implement Section 8 reporting provisions; to coordinate toxic substances information collection and retrieval systems; determine the sources of toxic substances entering the environment; carry out field measurements; and coordinate the various federal, state, and regional toxic substance control programs.

The Office of Testing and Evaluation (OTE) was established as the scientific institution responsible for testing recommendations and requirements as well as environmental and health hazard and risk assessments of new and existing chemicals.

The Office of Chemical Control (OCC) was created to be the focal point for regulatory policy for new and existing chemicals. This office contains the engineering and economic expertise necessary to evaluate technical feasibility and the economic consequences of contemplated control actions.

II. PROGRAM PRIORITIES

When TSCA was enacted, no significant organizational entity existed to implement it. As a result, highest priority activities by OPTS since passage have been those efforts necessary to build an institution capable of undertaking the major task of implementation. These efforts have included definition of organizational structure and function, staffing, and establishing operating procedures and policies. Thus technical service (obtained from ORD) has been one of the priorities of OPTS.

Considerable effort has also gone into establishing implementation strategies for all of the key aspects of TSCA. Particular emphasis during the early stages of implementation has been placed on those program aspects that are relatively unique to TSCA. These include evaluation aspects of TSCA (i.e. information collection and risk assessment) and the Premanufacture Notification (PMN) provisions of Section 5. Longer-term priorities include a greater emphasis on existing chemical regulatory activity.

To evaluate chemicals, OPTS has established a multi-stage risk assessment process designed both to take advantage of ad hoc information (e.g. Section 8(e) substantial risk notices), and to systematically select chemicals for the next level of analysis. In discrete stages, chemicals undergo increasingly detailed analysis with judgments made concerning the adequacy of the available information and the need for regulatory or non-regulatory control action. In later stages, the assessment process is designed to carry out the analysis of risks effectively enough to support regulatory actions under TSCA or other statutes.

III. PROGRAM STRATEGY

Each of the tasks outlined above requires the development and application of validated measures and techniques to assure quality. Data base precision and accuracy used for risk assessment and regulatory decisions will be achieved through a quality assurance program that covers personnel, methods, equipment, and data handling procedures. The quality assurance program is to be applied to each of these components individually as they function in an integrated research system.

OPTS will use the Section 8(b) inventory and Section 8(a) reporting information to provide sufficient information to systematically select chemicals entering the assessment process. If at any time a chemical or chemical class is deemed important enough to continue assessment, although key information is lacking, a Section 8(a) and/or 8(d) reporting rule, a monitoring study, and/or a Section 4 rule will be considered to obtain the necessary data.

In FY 78 and 79, much effort went into defining this process and initiating it for a selection of chemicals. In FY 80 and 81, the system should reach a steady state with certain chemicals feeding into regulatory processes as new ones enter evaluation.

To gather needed testing data, Section 8(d) rules are employed to identify unpublished existing studies. If testing is needed, Section 4 would generally be used to require industry to generate the necessary data. To implement Section 4, a series of test standards will be proposed through separate rulemaking for incorporation into test rules. TSCA requires that these standards be reviewed and revised as appropriately as possible, at least annually. Activities in FY 78 and FY 79 focused on an initial set of test standards for health effects testing. Test standard activities in FY 80 and 81 will stress revision and expansion of these health test methods, as well as the development of standards for chemical characterization, fate, and environmental effects testing.

The first test rules under Section 4 will be proposed in FY 80. The scope of the initial rules will be those chemicals recommended by the Section 4(e) Interagency Testing Committee (ITC). As soon as the Agency "catches up" to ITC, it is expected that Section 4 will be used to generate testing of those chemicals arising from the assessment process and categories of chemicals important to other programs and agencies.

With publication of the Section 8(b) Inventory of Chemicals in Commerce on June 1, 1979, the Section 5 new chemical premanufacture notification requirement went into effect. Most of the Section 5 efforts in FY 78 and 79 focused on laying the necessary procedural and policy foundation for the notification process. Interpretative rules containing a submission form have been proposed.

Although statutory authority to require testing is lacking, OPTS has been considering issuing new chemical testing guidance to clarify what approach to testing the Agency would advocate for new chemical producers. In FY 79 a pre-proposal discussion document was published in the Federal Register. Proposed guidance is scheduled for FY 80.

SECTION 2

OFFICE OF ENFORCEMENT STRATEGY

I. ENFORCEMENT STRAGEGY

The effective implementation of Section 4 is vital to the success of almost all other TSCA programs. Data submitted pursuant to Section 4 rules will assist the Agency in determining which chemicals should become subjects of further scrutiny through reporting or control regulations. Inspection strategies are being prepared to assure that the testing standards and rules are carried out properly by the testing facilities. Violations will be detected during these inspections and submitted test data performed by OPTS will be reviewed.

Section 5 represents an information-gathering mechanism crucial to the overall success of the TSCA program. The focus of the Office of Enforcement program concerning Premanufacture Notification regulations is the detection of "failure to notify" or "noncompliance" violations. Headquarters, acting with the assistance of OPTS, will target candidates for inspection. Inspections will be conducted primarily by the Regions, and enforcement actions will be directed primarily by Headquarters.

Section 6 rules are chemical-specific control regulations. To date, three chemical control regulations have been promulgated. The rules pertain to polychlorinated biphenyls (PCBs) and chlorofluorocarbons (CFCs). The major phases of the Section 6 enforcement program are as follows:

- Identify persons and facilities subject to the regulations.
- Notify such persons of the requirements of the rule and the potential consequences of violative behavior.
- Establish criteria governing the position a particular company occupies in an insepction-priority hierarchy.
- Develop guidelines for use by inspection personnel.
- Initiate compliance monitoring activities, including, if applicable, inspections, market sampling, literature review, and analysis of submitted data.
- Formulate a strategy for the prosecution of violators, including the ranking of violations and the development of penalty policy.
- Analyze data furnished through compliance monitoring activities and adjust enforcement strategy.

Section 7 authorizes the Administrator to seize and/or apply for equitable relief from imminently hazardous chemical substances or mixtures. The Office of Enforcement will not conduct an affirmative program to unearth emergency incidents. Rather, EPA will respond to imminent hazard situations when they are reported to the Agency. OE's involvement will focus on:

- the rapid and efficient processing of imminent hazard information
- the bringing of a Section 7 action
- the enforcement of any orders handed down by the appropriate judicial authorities

In addition to ongoing PCB and CFC compliance programs, OE will concentrate its FY 80 efforts on enforcing the inventory reporting requirements, Section 8(e) substantial risk notification requirements, Section 8(c) requirements regarding maintenance and reporting of allegations of significant adverse reactions, and Section 8(d) health and safety reporting requirements.

OE is currently working on a Toxic Substances Control Act Penalty System, which will serve to determine civil penalties against violators of the Act. The primary goal of the TSCA penalty policy is to encourage compliance with the Act, without setting penalties higher than is necessary to do so. The general penalty system is designed to achieve this goal while fulfilling the following requirements:

- Provide consideration of all of the penalty-affecting factors required by TSCA.
- Be structured enough to treat violators consistently and fairly.
- Be flexible enough to accommodate new and varied regulations to be promulgated under TSCA.
- Base penalty amounts on readily available facts and data.

II. ENFORCEMENT OBJECTIVES

The six main objectives set forth by the Office of Enforcement are: (1) defining methods for assigning priorities to chemical substances for investigations and regulations, (2) establishing procedures for testing and evaluating chemical hazards, (3) initiating actions for information gathering, (4) establishing mechanisms for the premanufacture notification of new chemical substances, (5) conducting laboratory inspections and case preparation in relation to data fraud, and (6) developing a coherent Agency-wide approach to toxic substances.

To accomplish these goals which relate to the Headquarters programs with oversight to the Regional programs, technical support from ORD will be needed in two sections of TSCA.

To meet Section 4 requirements, OE will need the analytical capability to analyze feed samples (obtained by inspectors while auditing an ongoing study) for test substance concentration. Pathology services for evaluation/interpretation of selected slides from a study will also be required by OPTS.

To satisfy Section 6 requirements, OE will need technical assistance from ORD in three main areas, namely:

- The development of standard analytical protocols for specific chemicals as they are identified for regulation. For existing Section 6 regulations, the development of methods for analyzing PCBs in mineral oil, waste oils, pigments and other media, and CFCs (fully halogenated chlorofluoroalkanes) in aerosol products.
- The development of multi-media environmental field sampling methodologies for PCBs and other controlled chemicals.
- The development of a rapid biological screening technique for PCBs and priority toxic chemicals.

SECTION 3

REGIONAL PROGRAM STRATEGY

I. REGIONAL OFFICE TOXIC SUBSTANCES CONTROL PROGRAMS

The Regional Offices reflect the Agency's focus on toxic substances control in all of their program implementation activities. This is seen in the ongoing Regional efforts in the air, water, solid waste, water supply, pesticides, and toxic substances media.

Direct TSCA-related activities include enforcement, information gathering to assist the Office of Pesticides and Toxic Substance's review of Premanufacture Notification, provision of technical assistance to industry and other affected groups in complying with TSCA regulations and voluntary chemical control programs, monitoring of TSCA Section 28 State cooperative agreements, etc. The Regional Offices are integrating toxic substances control activities in all media to maximize their program impact and operational effectiveness.

Effective enforcement of TSCA regulations, especially those promulgated under Section 6, requires the development of standard analytical methods for regulated substances in the specific media that will be encountered (air, water, soils, oil, etc.). Vigorous quality assurance is essential to ensure the validity of analytical data generated. Accordingly, methods development and definition of appropriate quality assurance considerations should commence at an early stage of regulation development to assure that they are fully established when the regulations become effective.

A prominent activity that spans many program concerns is the identification of and response to environmental and health related situations involving chemical substances. These situations are identified in any number of ways. They can be brought to the Agency's attention by the public, private industry, other governmental agencies, or our own activity in the Regional Office or at Headquarters. When identified, these situations must be evaluated to determine the nature and extent of the Agency's response. The Regional Office must decide if action is warranted and how best to achieve control. The process is similar to the analysis the Administrator must make to involve TSCA in a hazardous situation.

Although these situations can usually be characterized as problems with respect to one or more specific media such as air or water, they invariably involve presently unregulated substances. The first decision that must be made is whether or not the situation poses a health or environmental threat sufficient to warrant control. The Regional Offices often look to ORD and OPTS in this regard for technical assistance in the areas of environmental and health effects assessment and environmental monitoring. Where the appropriate surveillance and analysis capability is provided, this monitoring can be effectively performed by the Regional Offices. Often, however, resource limitations prevent extensive monitoring, and assistance is needed from ORD and/or other Headquarters program offices. This assistance could be in the form of direct ORD analytical support or ORD/OPTS contractor support. By close coordination of Headquarters contract and direct monitoring efforts and Regional Office requirements, monitoring activities can serve multiple needs.

Once a decision on the need for control has been made, appropriate action is taken. This action, when possible, will involve existing regulatory authority under the Clean Air Act, Clean Water Act, Safe Drinking Water Act, etc., where such action can effectively deal with the situation. When existing authorities are inadequate, the Regional Office will recommend consideration by the Administrator for such action under TSCA.

Finally, the Regions are faced with many and varied situations associated with disposal of toxic substances. Assistance from ORD for development and assessment of toxic substances disposal alternatives will be required.

Chapter Three
Research Strategy

SECTION 1

OVERVIEW

This chapter presents a detailed review of the research needs, strategies, and programs for the major areas of research conducted by EPA in support of TSCA: health effects research; environmental effects research; monitoring research; and environmental engineering technology research.

Chemical testing and assessment are the major emphases of all research efforts. For the health effects research component, the testing and assessment needs, strategy, and program are concerned with seven areas of study: (1) acute, subchronic, and chronic toxicity testing; (2) teratology and reproduction; (3) neurotoxicology; (4) mutagenicity testing; (5) carcinogenicity testing; (6) metabolism; and (7) epidemiology. Testing and assessment research for the environmental component will concentrate on environmental exposure and assessment techniques and methodologies. Monitoring testing and assessment needs fall mainly in the areas of toxic substance identification and control. Environmental engineering and technology will provide research on direct exposure and control options relative to the manufacturing, marketing, and use of chemicals.

Chemical specific concerns are also included in the research efforts, and are discussed, when applicable, at the end of each section.

I. TESTING SCHEMES

In contrast to the battery approach traditionally employed for drugs and pesticides, new chemical testing guidance and the generic approach to Section 4 testing are anticipated to consist of a tiered testing scheme.

The tiered or step sequence approach to testing is the preferred course, because unlike drugs and pesticides, commercial chemicals are not designed to be biologically active and have high human or environmental exposure. The tiered approach employs relatively quick and inexpensive tests to determine the need for more thorough studies. This approach offers the advantage of being able to direct scarce human financial resources to those chemicals and circumstances for which the greatest hazard or risk potential exists.

A subset of the tests in a generic tier scheme would probably be most appropriate for specific chemicals (such as those recommended by the Interagency Testing Committee) for which certain information generally already exists. Unfortunately, for most effects, only less than optimal tests are available which can be incorporated into a recommended or required tiered testing scheme. A tiered approach implies the need for two different types of tests, each with a specific set of characteristics.

Tests of the first type are often referred to as screening tests. The characteristics important for a screening test used under Section 4 or 5 of TSCA include:

- defined protocol
- high sensitivity (few false negatives)
- at least moderate specificity (discriminating)
- relatively inexpensive
- relatively quick
- relatively easy to perform
- reproducible
- readily interpretable
- broad applicability

Often tests with such characteristics simply do not exist for various effects. Fortunately, the state of toxicology is such that there are numerous concepts or systems that are possible candidates for future research. But, as described later, certain questions should be asked before selecting which to pursue.

Tests of the second type are often called evaluation or assessment tests. These tests logically follow screening tests and can be used to evaluate a chemical sufficiently to support regulatory decisions under Sections 5, 6, and 7 of TSCA and other statutes.

Evaluation tests should be reproducible, serve as a suitable model of human or environmental exposure, and be useful for risk assessment purposes (to the extent possible). For many, but not all effects, there are evaluation tests that could be employed under TSCA. Unfortunately these tests tend to be very expensive and time consuming. Few have sufficient data bases to evaluate fully their relevance to humans or the environment. Thus, more work is often needed on the assessment science for interpreting these tests than is needed for developing them. In some cases, new or less expensive tests are needed as testing recommendations are revised.

II. HAZARD ASSESSMENT

In its various assessment processes, OPTS faces a two-fold scientific challenge. First, it must be able to evaluate for regulatory purposes the results of tests that it prescribes. Second, it must be able to carry out hazard assessments on data from the potpourri of various tests that have been or will be performed on chemicals.

As much professional expertise as possible, both internal and external, will be brought to bear on OPTS hazard assessments. However, an enormous need still exists to improve our understanding of the meaning of chemical tests results. Professional judgment needs to be superseded by real data and fundamental knowledge.

In most instances, no good substitute for empirical information is available to evaluate the relevance of a test system. For example, to determine which professional judgment can be used to evaluate how important a non-rodent species is as a supplement to a subchronic rodent study, the best basis is actual experimental experience. Sometimes partial studies compiled and evaluated are sufficient to make such a judgment; however, preexisting information often needs to be supplemented before confidence is placed on a judgment.

Thus, OPTS sees the need to carry out additional experimental work to better understand the significance of existing and proposed test systems. OPTS suggests that an array of archetypal chemicals be agreed upon from which chemicals would be chosen for validation, standardization, and research studies on new and existing test systems. By doing so there will be a better basis to cross correlate test systems.

ORD research to support hazard assessment science needs is required by OPTS now and for the foreseeable future.

In some cases a sufficient basis exists to evaluate the dose-effect curve in a hazard assessment and to relate the test system to humans or the environment. Even in these cases, however, there is a need to evaluate as best as possible human and environmental exposure and exposure potential under a variety of different scenarios. This evaluation provides the basis for risk assessment and risk reduction analysis which are a part of regulatory decision-making under TSCA and many other statutes.

Exposure assessment involves many different types of analyses, including estimates and/or measurements of:

- environmental release
- environmental fate
- exposure through use
- exposure through distribution
- exposure through disposal

Some aspects of these analyses can be handled through the development and use of appropriate laboratory or field tests. Other aspects are best handled by the development of suitable models. Field monitoring is often needed to fill key data gaps and to evaluate the models used in exposure assessments.

Thus, OPTS has a need for much research into exposure assessment methodology, including:

- development and validation of certain fate test methods
- development and validation of certain monitoring methods
- development and validation of certain exposure and fate models

SECTION 2

TECHNICAL ASSISTANCE

Program needs for research and support from EPA's Office of Research and Development fall into four categories: technical assistance; testing methods; scientific foundations of risk assessment; and research on certain chemicals of interest· The early years of TSCA implementation will be building years, in which initial testing schemes and assessment approaches are to be established. Thus, the greatest needs for ORD support fall into the first three categories. As implementation matures and a greater fraction of program resources flow into regulatory activities under TSCA and other statutes, research and measurements on certain chemicals for which Section 4 testing is not appropriate will be increasingly important. Similarly, as more regulatory activities are undertaken, greater needs for research and support will be generated by the Regional programs and the Office of Enforcement, which will oversee their implementation.

The Office of Pesticides and Toxic Substances' highest priority for ORD support is for technical assistance. ORD has considerable experience and expertise on many subjects relevant to OPTS program activities. Included in these needs are technical input for and prior to Section 4 workgroup activities on test standard and test rule development. In addition, technical input is desired on proposed approaches to testing, monitoring, and various types of hazard and risk assessment under TSCA.

Finally, ORD technical comment on specific assessments is needed to assure the best possible product. This latter category may involve, for example, input of particular experts on certain Section 5 premanufacture notifications that raise issues related to their expertise.

We envision time and personal efforts of some of the best scientists in ORD. Because much of the ORD expertise relevant to OPTS's needs is located in laboratories remote from Washington, a significant allocation of travel dollars will be required for scientists to attend key meetings so that important details may be discussed directly.

ORD technical assistance in the areas of health/environmental effects assessment and monitoring is also a high priority Regional Office need. This assistance is often required to aid Regional decision-making in response to potential problem situations involving chemical substances.

SECTION 3

QUALITY ASSURANCE

I. QUALITY ASSURANCE PROGRAM

The environmental monitoring research program plays a dual role with quality assurance (QA) areas to provide both a review function for the Agency's mandatory quality assurance program and a research effort in the development of standardized methods andd protocols for monitoring testing programs.

Consistent with the Administrator's policy statement of May 30, 1979, when instituting the mandatory quality assurance program for the environmental monitoring program, all QA plans will be reviewed to assure that appropriate practices are continued or, when necessary, implemented.

In addition to implementing the mandatory QA program and associated research needs for environmental monitoring activities, the monitoring research program will assist OPTS in developing suitable guidelines for "Good Laboratory Practices" to guide industry in responding to testing required by TSCA.

When required, assistance will also be provided in the development of suitable quality assurance standards protocols. Many of the standardized methods have or will be developed under other environmental legislation. When such standards are unavailable for the purpose of

TSCA, they will be developed under this program. As test standards and guidelines are developed, quality assurance needs which are specific to individual protocols will be developed in phase with protocol development.

One immediately foreseeable need for FY-82 is the development of one or more multimedia quality assurance centers to serve all EPA environmental measurement programs. This need becomes increasingly evident as other EPA programs branch out into multi-media investigations to meet responsibilities under EPA legislative authorities. Other quality control needs will be incorporated into the program as they are identified.

II. FY-80 PLANNED PROGRAMS

- Develop a standardized protocol for sampling and analyzing asbestos in bulk material such as ceilings. Methods involve use of a polarized light microscope for identification and counting and X-ray diffraction for confirmatory analysis.

- Develop quality control tools as needed for specific protocols. Development needs to be phased with protocol development.

SECTION 4

HEALTH EFFECTS RESEARCH STRATEGY

I. OVERVIEW

The Toxic Substances Control Act of 1976 requires the Agency to address questions dealing with methods to be used in the toxicological evaluation of chemicals currently or potentially released to the environment. Therefore, it is necessary for the Office of Health Research (OHR) to work toward improving testing methodologies so that the confidence placed on test results, both qualitative and quantitative, may be increased.

Experimental animals have been used with a significant degree of success in testing chemical substances or products to predict their toxicity potential in humans. Historically, this testing has concentrated on endpoints of acute lethality. However, as it has become evident that the toxicity of chemicals may be delayed or cumulative in many instances, morbidity as measured by systematic histopathological examination has arisen as a consideration.

Toxic chemicals can impact a variety of target organs and a number of physiological systems. As more chemicals are tested, it becomes clearer that the systems which appear critical in acute toxicological tests may not be those which are affected in chronic tests. Classic incidences of this variation may be drawn from many chemicals, but the chlorinated hydrocarbons are perhaps the most pervasive examples. Chloroform, a chemical commonly found in drinking water, became prominent in medicine primarily for its effects on the central nervous system. The depressant activity of chloroform on the nervous system made it one of the first popular general anesthetics. Unfortunately, acute fatalities due to chloroform are invariably a result of this same activity. Through chloroform's continued use in medicine, however, it was soon found that late fatalities from chloroform anesthesia were the result of liver and kidney damage.

Chlorinated hydrocarbons used as pesticides are another example for which acute disturbances of the central nervous system lead to tremors, convulsions, and death, but long-term, low-level exposures result in liver and kidney hyperplasia, nodular formation, and ultimate oncogenic response. The bioaccumulation of many chlorinated hydrocarbons and the accumulation of chlorinated hydrocarbons in storage depots lead to continued toxic interactions long after acute or subacute exposure has ended. These extended interactions give entirely different responses. Animal experiments and human experience have repeatedly confirmed that acute toxicity is a poor predictor of the chronic toxicity of a wide variety of chemicals.

A second feature of chemical toxicity is that the route by which a chemical contacts the animal can often dramatically affect the nature of its toxicity. For example, the lung is often the target organ of inhalation exposures to a chemical, whereas it would often not be a taget organ if the same chemicl were encountered in the diet, drinking water, or other media. A chemical contacting the skin may produce a local reaction rather than the systemic action which might occur if the chemical were taken internally. Specific examples of the dramatic influence the route of exposure can have on chemical toxicity include: the pronounced central nervous system toxicity observed with inhaled elemental mercury and the absence of such toxicity by the oral route; and the lung proliferation noted on oral ingestion of paraquat and the absence of such effects from dermal or inhalation exposure.

Results obtained from testing chemicals in different species have made it increasingly evident that unexpected differences exist between species and/or sex sensitivities and susceptibilities. In certain instances, the bases for peculiar across-species or sex variability have been resolved: different mechanisms may be involved in the metabolism of a chemical in different species; or certain hormonal systems may be involved in the toxicity observed. However, no general basis for such differences has been established.

Finally, advancements in the understanding of certain types of toxicity have allowed the development of presumptive tests for some types of chronic toxicity. At present, these developments are best exemplified in the area of chemicl carcinogenesis. The use of the somatic mutation theory of chemical carcinogenesis has allowed the development of a number of genetic assays in bacteria to be used as qualitative tests for chemical carcinogens. The understanding of toxicological effects in mechanistic terms is so poor in most areas, however, that such methodologies have limited application outside the area of chemical carcinogenesis and/or mutagenesis testing.

II. TESTING AND ASSESSMENT

At the request of the Office of Testing and Evaluation (OTE), this section has been organized in a manner corresponding to OTE's research program. This organization leads to certain lapses in logic; for example, the redundancy in discussing such issues as species differences creates areas of artifactual overlap such as behavioral teratology, etc. However, this organization does lend itself to more direct establishment of functional contacts between OTE and the corresponding researchers within OHR. Implicit in this organization is the weighing of priorities across these research areas, allowing for (in extreme cases) the abolition of one research area to meet a higher priority as perceived by the Program Officer in another area.

The seven research areas discussed in this section are:

- Acute, subchronic, and chronic testing
- Teratology and reproduction
- Neurotoxicology
- Mutagenicity testing
- Carcinogenicity testing
- Metabolism
- Epidemiology

In the last analysis, the most cogent scientific evidence upon which the regulatory function of OPTS can be predicated derives from direct epidemiological study of the impact of a given exposure upon human health. However, such an approach must be tempered by full appreciation of existing limitations in epidemiological technique when applied to the problems confronting a regulatory agency. Nevertheless, in research planning the pre-eminent role of epidemiological study merits full emphasis.

Finally, this section addresses the question of toxicity testing costs and effectiveness, which are of fundamental importance to the enforcement of TSCA. As toxicological endpoints are increased in number or the length of experiments is extended, the costs of testing chemicals increase substantially. Since acute toxicity is not a predictor of chronic toxicity, the question is whether or not subchronic toxicity is an accurate predictor of chronic toxicity. If so, what mathematical functions describe the differences between subchronic and chronic toxicity to various organs? If a good fit can be achieved, what should the minimum duration of subchronic testing be to predict adequately toxicity observed over a lifetime in all target organs? Similar problems exist in the more specialized areas of toxicological testing. In cases where a latent period is definitely involved in the development of the disease (e.g. cancer), the researcher would like to determine if some constant relationship exists between precursor lesions and the development of the life-threatening phase of the disease. There are partial answers to some of these questions, but a data base has not been developed which contains sufficient information to support testing regulations and guidelines. Further work is needed to establish many of the parameters required to establish an efficient means of assessing all toxicological endpoints.

A. ACUTE, SUBCHRONIC, AND CHRONIC TESTING

1. Background and Status

Toxicity testing falls into three basic categories, depending primarily on the duration of exposure. Acute toxicity can be defined as the adverse effects which occur following exposure to a test agent for 24 hours or less. This definition provides for the 24-hour exposure often used in dermal procedures and the 1- to 8-hour exposures often used in inhalation procedures. Subchronic toxicity procedures are designed to detect adverse effects that may occur during repeated exposure over a few days to a few months (usually to 90 days). The dosage levels used are usually intended to be sublethal and directed towards detection of specific target organ or system lesions. Subchronic studies are considered essential to the design of lifetime studies (e.g. chronic and/or oncogenicity studies). Chronic toxicity studies are generally regarded as involving exposures ranging in duration from 6 months to the lifetime of the test species. Generally, the classical chronic toxicity test is supported as the only available experimental approach for assessing long-term human health hazards. The basic tenets inherent to all toxicological testing are: (1) use of multiple species; (2) long- and short-term testing; and (3) consideration of the route(s) of exposure. There is enough historical perspective on acute, subchronic, and chronic testing to justify the application of these testing procedures to new chemicals and products immediately.

The major practical difficulty in acute, subchronic, and chronic testing is determining the point at which redundancy of testing becomes cost-ineffective. For example, given that species differences exist in toxic responses to toxic chemicals, how many species must be tested in acute, subchronic, and chronic phases before one gains a level of confidence in the overall test results?

A second difficulty with utilizing historically-founded toxicological testing methods is the question of what toxicity escapes detection. In some respects, the historical record of the drug industry is not comforting. Too often, toxicities dissociated from the desired therapeutic effect of a drug (ruling out simple overdose or exaggerated therapeutic effect as the mechanism) have been discovered in humans rather than in pre-market toxicological testing. Such examples abound and in large part are responsible for the development of some of the specialized areas of toxicological study (with the notable exception of mutagenesis since there are no known examples of a chemical mutagen in humans). The current emphasis on teratology had its genesis in the human experience with thalidomide. Liver and kidney damage associated with halogenated organics such as those used as anesthetics or pesticides serve as another example of toxicities first discovered in practice. The toxicity of the anthracycline antibiotics for the heart was also first discovered in humans, even though their use in medicine is quite recent. Most of the problems associated with the use of oral contraceptives are becoming evident through human epidemiology rather than through animal experiments. More recently, the epidemiological literature has suggested that a chemical used in the treatment of atherosclerosis improves the symptoms of the disease but shortens the life span of patients. In view of the vast number of chemicals entering the market as drugs, these and similar examples undoubtedly represent a small fraction of the chemicals that are subjected to toxicological testing procedures. However, they do demonstrate some of the limitations of the current methodology used in toxicity testing.

Trade-offs between risks and benefits from environmental chemicals are fundamentally different from those considered for drugs and occupational exposures. The taking of drugs is for the individual's personal benefit (i.e. therapeutic reasons) and is generally voluntary, making some risk-taking acceptable. Occupationally, an individual does at least receive compensation, which allows a personal means of weighing risks and benefits. However, what level of risk-taking is acceptable with environmental chemicals from which the individual may not derive any direct personal benefit? Traditional toxicological tests will undoubtedly still serve to define hazards; however, the demands for accurate risk assessment have become more critical in the environmental toxicology area because the impact of a chemical's effects on a large population (as opposed to the individual) must be wieghed against benefits attributable to the chemical. This difference makes the definition of the dose-response characteristic of chemically-induced disease processes and the responses of sensitive populations of much greater importance. Thorough understanding of the quantitative and qualitative variables operating in chemically-induced disease states is essential for accurate and equitable risk/benefit analyses.

Much of the difficulty associated with general toxicological testing is the question of how complete a picture is gained from the histopathological examination of major organs and tissues. Without doubt, histopathological examination is the most generalized and cost-effective technique that can be applied to long-term testing procedures. However, what is generally observed is simply evidence of cellular death and resultant tissue necrosis. Such changes are late manifestations of functional disturbances which can often be detected biochemically, physiologically, and on an ultrastructural level far prior to and at lower exposures than histopathological changes. The major source of false negative results is the extent to which histopathological techniques are insensitive to functional disturbances.

A second reason for false negatives is the inability to include considerations of every possible endpoint in a testing protocol. The pursuit of variables must often be based on consideration of the documented toxicity of related chemicals to prevent the cost of a test from being prohibitive. This technique has two weaknesses. First, structure-activity relationships have very limited application in toxicity testing since subtle changes in chemical structure often have dramatic and unpredictable effects on toxicity. The only real successes achieved with this technique have been situations in which pharmacokinetics have limited biological effect or very specific chemical receptor interactions were being dealt with. The second weakness is that testing of analogues is rarely complete. For example, cardiovascular diseases are the major cause of death in human populations, yet in toxicological testing very little consideration is generally given to the processes which give rise to cardiovascular disease. Depressed immune function is a second example. Damage is undoubtedly done to the organism in this case, but the morbidity and mortality that result arise from indirect causes. This damage would not be readily apparent histopathologically. Neither is the damage likely to be recognized as resulting from a chemical instead of a microbiological etiology, if it does occur in a human population.

The opposite of the problem posed above (i.e. false negatives) is the problem of false positives. Traditionally, when extrapolating data to humans, only data obtained from the most sensitive species tested (usually limited to mammalian) are utilized unless other ancillary data clearly demonstrate the species inappropriate. In general, data are not sufficiently complete to allow determination of the most appropriate species at the time a decision is made. This in many cases undoubtedly results in regulatory decisions being made on the basis of an exaggerated risk estimation, distorting the cost/benefit ratio upon which the regulatory decision must be made. However, in the absence of substantive data to clearly establish the most appropriate species, the decision is generally made to err on the side of increased public safety by using data from the most sensitive species.

Thus the key questions surface as: (1) the appropriateness of effects on biological and animal models to humans; and (2) how to model accurately the extrapolation of these effects to humans. These questions are of primary importance to the Agency. Unfortunately, no basic scientific effort to design convenient models of toxicologically-induced human disease processes has been undertaken outside of the chemical ccarcinogenesis area. In general, what efforts have been made have been specific to the investigation of single chemicals. This area of study has not developed because the substantial resources necessary to develop this data base have not received a high priority. Instead, resources for environmental toxicology research have been allocated along the lines of pursuing the effects of single chemicals with the goal of establishing maximum contaminant levels (MCL's). With TSCA legislation, a coordinated effort to establish a generalized methodology for across-species extrapolation in quantitative as well as qualitative terms is of very high priority.

2. Research Strategy

The Office of Research and Development (ORD) research strategy on health effects research supporting TSCA must be sharply focused in order to be effective. Many nonscientific issues will be key considerations in the regulatory posture ultimately arrived at by the Agency; for example, economic considerations surrounding the particular chemical being tested, the availability of suitable alternatives, and the size of the population likely to be impacted. These considerations will and must be weighed against harm to humans and the environment in order to arrive at a sensible and defensible regulatory stance. Therefore, it is essential that testing strategies in the health area produce the best possible estimates of a chemical's ability to produce human disease. Furthermore, this evaluation must be done in a cost-effective manner since, in many cases, the cost of testing alone could exceed the projected economic benefits that may be derived from a chemical.

The fundamental questions which must be addressed over a wide area of disciplines are:

- What is the full range of human disease states that could result from exposure to environmental chemicals and chemical classes?
- Can we define the appropriate test systems and/or animal species that may be employed in a cost-effective manner to detect reliably chemically-induced disease processes?
- What are the critical factors (e.g. metabolism, pharmacokinetics, repair processes) in the handling of a chemical or the responses of different species that impact quantitative extrapolation between species?
- What is the place man occupies in the range of sensitivities expressed by various species to particular types of toxicity (i.e. interspecies comparisons of intrinsic sensitivity)?

Research must determine what the most significant endpoints addressed in toxicological studies should be. In addition, it must establish what types of toxicity are observed when representatives of major chemical classes are given. The literature available today is not particularly useful in answering these questions because in the past chemicals have usually been studied for their effects on particular organ systems (e.g. chlorinated hydrocarbons and liver necrosis), and the pathology to other organs and tissues has generally been ignored. Efforts should be directed at detecting damage at the biochemical, physiological, and ultrastructural levels which can be correlated with functional deficits as well as histopathological examination of major organs. A critical assessment of what organs are specifically impacted at lower doses than others will allow development of a maximally cost-effective test protocol.

The similarities and differences between humans and experimental animals on a biochemical and physiological basis must be investigated. Attention should focus primarily on animals which would fit logically into testing protocols rather than simply on "man-like" animals. Most man-like animals could never be employed in large-scale testing because of their limited numbers and extremely high cost. This effort, then, should be designed to uncover the actual physiological and biochemical differences involved in the spurious results given by a particular species, so that the required characteristics for a human response may be specified. This type of information across multiple endpoints could eventually allow specification of a single species for testing chemicals with particular characteristics. These data could replace the arbitrary specification of two to three species now utilized as a means of reducing the risk of false negatives. In addition, these data would serve as a basis for rejecting positive data developed in an inappropriate species historically.

The appropriate species or test systems (in terms of the qualitative similarity of their responses to toxic chemicals) must then be studied with regard to the quantitative relationships between their responses and those of man. This area has the largest impact on the regulatory process and is the least well understood. At present, the arbitrary assignment of a safety factor (ranging from 10- to 1000-fold) to results obtained in the most sensitive species is the only defensible position and is the most prudent course from a public health point of view. However, it is highly probable that many very useful chemicals are and may be kept out of commerce on this basis. Less probably, but still possibly, this lack of knowledge and the lack of quantitative extrapolation models could lead to the acceptance of a substance *more toxic to humans* than substitute, particularly if the two chemicals produce different toxic effects. Man could be more sensitive than the test species to one type of toxic effect and less sensitive to another, leading to false conclusions of the relative hazards of two alternative chemicals.

To complete a risk assessment, some critical knowledge is necessary concerning the development of a disease process with doses, particularly with low doses. Is the process simply linear with dose as is assumed with cancer, or is there a threshold below which no effects occur? In either of these cases, how can the variability in sensitivities produced by predisposing risk factors be taken into account in extrapolation?

3. Research Program

The research and development (R & D) toxicology program supporting the Agency's toxic substances regulatory efforts will concentrate on the development and validation of test systems and animal models that serve as predictors of human disease processes which may be potentially impacted (directly or indirectly) by environmental chemicals. The major areas of research will investigate: (1) the development of methods capable of evaluating the responses of entire systems to a toxicant insult (i.e. the cardiovascular system, the immune system, the reproductive system, the gastrointestinal system, etc.); and (2) the development of methods sensitive to specific target organ toxicity (i.e. liver, kidney, heart, lung, skin, etc.). Since the former are the broader tests, it is anticipated they will eventually form the core of screening or first level tests, whereas the latter tests would be more specific and confirmatory in nature. In each of these cases it may be necessary to develop a data base to establish the most appropriate species. Specific research needs may be divided into those needed in acute toxicity testing, subchronic toxicity testing, and chronic toxicity testing.

a. Acute Toxicity

Code #	Immediate Research Goals	OPTS Priority*
A-1	● Need to standardize the acute inhalation toxicity protocol so that is is comparable to the acute oral, dermal, and eye models.	1
	Intermediate Research Goals	
A-2	● Continue "Round-Robin" testing of all acute procedures to determine if across laboratory variation falls into an acceptable range.	3
A-3	● Support program for enhancing sensitivity of classical approaches (e.g. use of pathological bacteria introduced into animal lungs following exposure to common pollutants as adjunctive studies).	2
A-4	● Develop methodologies for detection of asthmatic type sensitization.	1
	Long-Range and Basic Research Goals	
A-5	Conduct basic research on animal and human skin which would lead to a fundamental understanding of factors which influence permeability and/or irritation.	2

* Ranking of priority: (1) High - (5) Low

A-6		Conduct basic research on animal and human lungs which would lead to fundamental understanding of factors which influence local effect and/or absorption (e.g. particle size, solubility, reactivity, etc).	1

b. Subchronic Toxicity

Immediate Research Needs

A-7	●	Review existing data on various parameters used in present protocol for reliability and predictability (e.g. urine analysis, certain elements of the hemogram, and clinical chemistry). The aim of this review would be to evaluate the usefulness of certain commonly used tests.	1
A-8	●	Introduce new parameters for inclusion in protocols (e.g. Serum Ornithine Carbamyl Transferase (OCT) as a liver response test for exposure to certain organic solvents).	1
A-9	●	Determine how much useful information a 90-day test would contribute as opposed to a 28-day test or a 7-day test.	2

Intermediate Research Needs

A-10	●	Establish the minimum duration of subchronic toxicity tests which can be utilized to predict chronic toxicity for chemicals. (Shorter-term tests must account for decreased lifespan from nonspecific organ toxicity).	1
A-11	●	Determine the relevance and dependability of in vitro systems as predictors of target organ toxicity in vivo.	3
A-12	●	Provide a scientific basis for making quantitative extrapolations from data obtained with experimental animals to effects predicted in man.	2

A-13	●	Characterize toxicity to different organ systems. Also characterize toxicity induced by different mechanisms with respect to those mechanisms' reversibility, cumulative nature, characteristics of biochemical interactions, and the mathematical relationships involved in the damage function at different levels of organization.	1
A-14	●	Provide systematic investigation and characterization of representative chemicals from major classes of environmental chemicals concerning their target tissues, organs, or systems. Test models used for extrapolation of data to man for their generality.	1
A-15	●	Systematically investigate the effects of chemicals on target organs or systems involved in major human diseases to determine the extent to which toxic chemicals may impact those disease processes (e.g. cardiovascular diseases and the immune system).	1
A-16	●	Develop organ function tests applicable to subchronic tests (e.g kidney and liver function as opposed to static tests). The sensitivity of the glucose tolerance test versus blood glucose and/or urine glucose have been amply demonstrated.	3
A-17	●	Expand the test protocol to include endocrine effects (e.g. thyroid effects through measurement of PBI, T_3, TSH, etc.).	1
A-18	●	Review diagnostic procedures used in human medicine for applicability to animal protocols.	2
A-19	●	Examine pre-existing studies to determine how helpful nonrodent data are.	2

Long-Term and Basic Research Needs

A-20	●	Develop predictive models for safety evaluation in certain subpopulations at high risk (e.g. persons with inborn errors of metabolism, the chronic kidney	3

diseased population which has approximately 10 million members in the U.S., and persons having sensitivity to kidney toxicants).

A-21 ● Determine relevance and dependability of *in vitro* systems as predictors of target organ toxicity *in vivo*. 4

A-22 ● Provide systematic investigation and characterization of representative chemicals from major classes of environmental chemicals to identify target organs and to test the generalities of models used for extrapolation of data to man. Is the use of a nonrodent species *essential* for proper safety evaluation? Is the use of the NOEL proper in determining margin of safety (M.O.S.)? 2

c. Chronic Toxicity

Immediate Research Needs

A-23 ● Initiate discussions with NTP/NCI for investigating feasibility of expanding their chemical carcinogenesis bioassay to include non-oncogenic chronic effects (primarily additional dosage levels). 1

Intermediate Research Needs

A-24 ● Clarify those parameters in Levels I and II which would trigger need of chronic testing. 1

A-25 ● Undertake analysis of the NCI bioassay data base and other data bases which may support TSCA chronic health effects standards. 1.5

Long-Term and Basic Research Needs

A-26 ● Develop altered protocols for Level III testing using stressed animals (e.g. lower target organ function). 3.5

A-27	●	Research into the mechanism of action of target organ pathology.	2.5
A-28	●	Research to validate the ability to predict the qualitative and quantitative response to Level III tests and human populations from Level I and II tests.	3
A-29	●	Epidemiologically validate non-oncogenic chronic toxic responses in human populations.	4

B. TERATOGENESIS TESTING AND REPRODUCTIVE TOXICITY

1. Background and Status

The developing embryo and/or fetus is known to be vulnerable to a wide variety of agents which effectively interfere with normal development and function. This vulnerability has been demonstrated both in the laboratory and in the environment. A series of tests have been standardized and are currently utilized to assess the potential of agents to induce prenatal toxicity. These tests involve the response of pregnant mammals to the test agents during the period of greatest embryonic organogenesis. The pregnant animals are sacrificed shortly before term, and the fetuses are examined for soft tissue and skeletal anomalies. These standard tests suffer from several significant shortcomings, including the time and expense involved in performing them: the difficulties in assessing the importance of experimental effects in terms of the human population; the problem of extrapolating test data to form some estimate of potential risk to the human population; and the lack of a testing framework which will identify functional deficits which may only appear postnatally.

The reproductive system is known to undergo several critical periods during development. These include organogenesis, sexual imprinting, morphological development, puberty, functional reproduction, and decline in reproductive activity. The hypothalamic-pituitarygonadal axis is vulnerable to a wide variety of agents. Assessment of the reproductive system in the past has generally been limited either to the dominant-lethal evaluation in males, or evaluation by output from "three generation" type data, (such as fertility index, gestational index, viability index, and lactational index) in females. These types of assessment fail to evaluate specific physiological alterations. In addition, they are time-consuming, expensive, insensitive, and not necessarily predictive of effects in humans.

2. Research Strategy

a. Teratology

A primary aim of research in teratology is the scientific support for and development of tests for evaluating chemicals for human teratogenic potential. Faced with the task of screening large numbers of chemicals for teratogenic potential, current testing methodology suffers from some severe drawbacks. No cost-effective screening tests are available for the assessment of this health effect, since the "definitive" test used for teratogenic hazard assessment is the two-species animal study. This study is expensive, time-consuming, and measures only structural anomalies which must be extrapolated to indicate an impact on humans. Clearly, additional research in the area of teratology testing is required.

Of primary importance in teratogenicity testing is the development of a Level I (i.e. screening) test for teratogenic potential. The demands on such a test are great since teratogenicity may be the consequence of one or more separate effects of a chemical agent on a biological system during a "critical" period of development. Possible solutions to this need may be in the development of a battery of short-term tests for various suspected mechanisms of teratogeneis. This battery would include tests for mutation, chromosomal non-disjunction, altered nucleic acid integrity or function, lack of chemical precursors of substrates, altered energy sources, change in membrane characteristics, etc. These tests might involve in vitro cell, organ, or embryo culture techniques. This approach is a complex one; however, the potential for missing a true human teratogen will have to be weighed against the possible savings of time and resources by use of such a screening battery.

Although desirable in a tier scheme, no Level II (i.e. confirmatory) test is available for use at this time. A possible candidate for this level of testing is an in vivo embryo/fetal toxicity test which is now in the process of being validated with known animal teratogens. This test requires breeding and dosing regimes similar to a two-species study, but requires only the weighing and counting of offspring at birth and 3 days later. Positive results in this test (a decrease in viable litter size after 3 days) would be taken as evidence for teratogenic potential, requiring a two-species study for hazard assessment. Preliminary evaluation of this test indicates a high percentage of "true positives," but an indepth evaluation of this test will be required to recommend its use in an EPA tier scheme.

At present, EPA's test scheme suggests a two-species teratogenicity study on all chemicals for which exposure, production, structure and/or biological activity relationships, epidemiology, or other existing biological data dictate further tests toward the evaluation of this endpoint. Other data supporting the use of this type of study come from reproduction or metabolism studies where biological effects or chemical products (metabolites) might increase suspicion of teratogenic potential. Further research is needed to strengthen these aforementioned correlations. In addition, the development of extensions of this test for the evaluation of "late" effects including growth retardation, behavioral effects, and perinatal carcinogenicity have been recommended.

The research strategy in the area of teratology will address a number of basic problems faced in any attempt to formulate regulatory policy based on experimental data.

Interpretative Problems: A variety of embryonic and fetal changes observed in experimental data derived from current test protocols, although shown to be clearly compound-induced, are not understood in terms of their biological significance. Examples of these non-teratogenic effects include decreased fetal weight, the occurrence of wavy and/or supernumerary ribs, and delays in the development of various organ systems (e.g. enlarged renal pelvis and enlarged cerebral ventricles). These types of data are currently being submitted to the

Agency, and the use of these data depends on the understanding of their toxicological significance. Research should therefore be directed towards optimal utilization of the data derived from current testing procedures.

Extrapolation Problems: In any governmental agency with a regulatory mandate, the most important endpoint of many toxicology studies should be the significance of the experiment's effects to the human population. In the field of teratology, relatively little attention has been paid to problems associated with extrapolation of data between mammalian species, in both the quantitative and qualitative sense. In order to assess comparative species sensitivities to different agents in terms of the types of defects seen and their relative incidences, research should be directed toward dose-response relationships in diverse laboratory species. A key part of such an effort should be the detailed analyses of human data and the comparison of such data with data developed in the laboratory setting.

Method Improvement Problems: Current standard test procedures are not concerned with the fate of the animal after parturition. It has been demonstrated that several compounds, when administered during the prenatal phase of development, produce toxicological manifestation apparent only in the postnatal animal. Research is needed for postnatal sequelae of *in utero* exposure to compounds. This research should be directed at assessing permanent alterations in the hemostatic functioning and reserve capacity of all major organ systems.

Resource Utilization Problems: Current teratogenic screening procedures require the input of scientists and highly skilled technicians and 3 to 5 months of experimental work. In addition, the cost of a standard test in two species is approximately $35,000. As such, our current capability for assessing the teratogenic potential of compounds could quickly be outstripped by the testing that may be required under TSCA. There is a need, therefore, to develop test systems which will enable regulatory personnel to prioritize the testing of compounds by standard procedures. These tests should ideally reduce the requirements of technical expertise, as well as time and financial commitments involved in the standard assays. Research should be directed into the development, validation, and utilization of short-term test systems which will accomplish the above objectives.

b. Reproduction

Certain chemicals will have no data available from which reproductive hazards can be assessed. Innovative chemicals for which production figures cannot be projected adequately and high exposure chemicals of low production could possibly be inhibited by requirements for testing. Inexpensive tests are necessary for the testing of these types of chemicals under Sections 4 and 5 of TSCA.

Testing for Section 4 and 5 chemicals is organized in a tier-wise fashion, progressing from general evaluation tests which are least predictive (such as structure/activity relationship tests) to tests which are of more predictive value (such as a reproductive test in an animal species).

In the lowest tier, structure/activity relationships and biological activity of known or suspected potential are used to predict potential for reproductive effects. Improvements in available testing methods are needed to detect these relationships. The next higher level of tests should include a screening test (not currently in the tier testing scheme, but projected if suitable tests become available). A screen should be predictive of effects on fecundity; however, because of the lack of suitable methods, the screen may be limited to fertility or other specific factors in reproduction. Positive results from the test should either trigger reproductive testing or be of sufficient validity to be useful in hazard evaluation or in risk assessment and regulations. The reproductive test which could be triggered by the screen needs considerable improvement. Subchronic and chronic tests can trigger reproductive testing. Subchronic studies are not always predictive of physiological effects which may disrupt reproduction and which may be detected by the pathologist associated with the study. Improvements in the predictability of these tests for reproductive effects are needed.

The research approach in developing and assessing rapid, sensitive, and cost-effective reproductive tests must address a number of basic problems.

Interpretative Problems: Compound-induced alterations with no apparent functional reproductive effects have been observed in sperm count, morphology, viability, and motility. In addition, changes in the normal serum hormone concentration during development have been seen without apparent changes in functional reproduction. The significance of these and other subclinical indices in the reproductive life of the animal have yet to be evaluated. Research efforts should be directed toward optimal utilization of these data.

Resource Utilization Problems: Current procedures to assess reproductive function require 6 months to 1 year and highly skilled technical assistance. The reproductive testing that may be required under TSCA would be unrealistic using these current test procedures. Therefore, the research effort should be directed toward the development and validation of test systems which require a minimum of time and resources and allow prioritization of compounds for the standard reproductive test procedures.

Method Development/Assessment Problems: Concomitant changes in other functional systems should be evaluated for their potential to predict reproductive effects. Sexually dimorphic behavior patterns in model species is an area where further investigation into the possible predictive value of deviations from the norm may be of value. The role of postnatal exposure to toxic agents through the milk should also receive attention since it is known that this route of exposure may be of considerable importance in the toxicity of lipophilic compounds.

3. Research Program

a. Teratology

Code #		Immediate Research Goals	OPTS Priority
B-1	●	Validate the proposed short-term *in vivo* screen by the testing of a significant number of diverse compounds of known teratogenic potential.	1

B-2	●	Evaluate other proposed short-term screens, including the growth of an embryo and/or embryonic tissues in culture.	3
B-3	●	Compare the responses of rodent and nonrodent species to agents administered during gestation. Data from humans should be included.	1
B-4	●	Conduct studies of dose-response relationships to specific agents in different species.	3
B-5	●	Develop and validate behavioral teratology testing procedures in rodents.	1
B-6	●	Acquire data on the background malformation rates, inherent susceptibilities, and resistance to certain chemicals for the various species and strains.	4

Intermediate Research Goals

B-7	●	Conduct studies to determine the significance of various manifestations of fetal toxicity (excluding gross terata) on perinatal viability and function. These experiments will attempt to measure the potential of agents to prenatally induce postnatal functional alterations in the absence of gross terata. Areas of study will include: hepatic function and metabolic patterns; central nervous system growth and function including selected behavorial parameters; cardiac function, renal function, and resistance to stress.	1
B-8	●	Evaluate the effects of maternal toxicity on the outcome of embryonic and fetal development.	1
B-9	●	Study the potential of diverse agents to act synergistically and result in perinatal function. An example of this type of study would be the simultaneous administration of fetotoxic agent and a teratogen.	3
B-10	●	Develop biochemical markers of postnatal development that may be used to assess	2

developmental delays of major organ systems.

Long-Range Goals and Basic Research

B-11	●	Conduct studies to elucidate the basic mechanism's response for perinatal dysfunction. Specific areas of investigation would include: histopathological development of terata; correlation of biological actions of agents with perinatal effects; and biochemical and physiological causes of perinatal dysfunction.	1
B-12	●	Study the potential of agents to induce dominant non-lethal mutations during the male spermatogenic cycle as evidenced by the production of terata after breeding with untreated females.	2
B-13	●	Assess the utilization of ultrasonic vocolizations in neonatal rodents as an indicator of the general health status of animals to toxic substances during *in utero* development.	2
B-14	●	Study the effects of diet, including selected deficiencies, on perinatal response to agents.	4
B-15	●	Study the effects of *in utero* exposure on the ontogeny of senescence.	3

b. Reproduction

In the area of reproductive toxicity, efforts will continue to develop an acute (14-day) and a subchronic (30-day) reproductive screening procedure applicable for regulatory programs. These efforts will incorporate modern and sophisticated reproduction, physiological, biochemical, morphological, and functional methodologies.

Immediate Research Goals

B-16	●	Develop a reproductive screen which is value-effective in screening for: sperm motility, number, and viability; and ovarian cyclic function, ovum viability, and uterine impairment.	1

Intermediate Research Goals

Using current acute dosing regimens and selected compounds, studies will evaluate short-term response of the hypophyseal-gonadal axis through the use of the:

B-17	●	FSH, LH, FSH-RH, LH-RH, and steroid hormone (testosterone, estrogen, etc.) profiles in males and females	1
B-18	●	*In vivo* and *in vitro* HCG stimulated Leydig cell testosterone production	1
B-19	●	*In vivo* and *in vitro* pituitary extract stimulated testosterone production	2
B-20	●	Alterations in sexually dimorphic patterns including anatomical and behavioral differentiation, fertility, fecundity, and the ontogeny of infertility	1
B-21	●	Morphologic parameters, i.e. testes, ovarian, and accessory gland weight	1
B-22	●	Histological parameters, i.e. pituitary, gonodotrophocytic, and hypothalamic cytologic alterations	1
B-23	●	Effects on sperm production and quality, i.e. number (vas deferens and epididymal), viability, morphology, motility, and capicitation	1
B-24	●	Physiology of lactation and the transport of toxic compounds to sucklings	1
B-25	●	Evaluation of the effects on the estrus cycle	2

Long-Range Goals and Basic Research

Short-term response of the hypophyseal-gonadal axis will be evaluated through the use of:

B-26	●	Interaction of other endocrine physiology with reproductive function	1
B-27	●	Identification of optimal species for specific reproductive testing procedures	2

C. NEUROTOXICOLOGY

1. Background and Status

Despite man's long association with chemicals which adversely affect the nervous system, regulatory agencies are just now focusing attention on the study of neurotoxicology. This focus includes the recognition that neurotoxicological evaluation is an essential component in a comprehensive toxicology program. Many chemicals, which are derived from a variety of sources (environmental, occupational, food and drugs, etc.) and have a variety of intended uses (additives, pesticides, industrial chemicals, and which enter the body by a variety of routes (air, water, food) exert toxic effects on the nervous system. Therefore, a systematic investigation of neurotoxicity, including the development of short-term tests, is essential to all government agencies concerned with the protection of human health. Section 4 of TSCA specifically calls for such research; "the health and environmental effects for which standards for the development of test data may be prescribed include . . . . Behavioral Disorders, cumulative or synergistic effects and any other effect which may present an unreasonable risk or injury to health or the environment." A comprehensive neurotoxicology program is needed to investigate chemically-induced changes in nervous system function at all levels of organization, including functional and structural. This multi-disciplinary approach is essential, especially for the cross-validation process which will allow for the development of short-term tests which are rapid, sensitive, and cost-effective. The data base for implementing such testing procedures, including validation, does not exist.

The development of a tier testing scheme for multi-disciplinary neurotoxicity testing is in its early stages of development. The current tier testing scheme consists of acute and repeated exposure dose-response experiments. In the absence of specific knowledge about a chemical's targets within the nervous system, acute tests will consist of an 1-hour locomotor activity test and a functional observational battery. Where existing data or acute test results indicate, specific behavioral or neurophysiological function tests (e.g. motor nerve conduction velocity) will be combined with general neuropathology tests in the repeated exposure testing. Where warranted, neurochemical tests will also be included in the repeated exposure testing. Other special tests warranted by existing information on specific chemical classes will be required on a case or class basis.

The status and source of the proposed tests illustrate the problems in this area that EPA's Research Program should address. These problems include the following:

- General types of tests have been proposed, e.g. tests of locomotor activity or functional test batteries, but specific tests for these categories have not been systematically evaluated or validated for chemical toxicants. Our need, then, is both to validate explicit tests of locomotor activity and to evaluate empirically the relative sensitivities of different tests of locomotor activity.

- Specific tests of general functions referred to above, or tests of more specific neurological functions (e.g. conditioned reflexes or motor nerve conduction velocity), have generally been used to evaluate drugs often designed for neurological effects or to evaluate one chemical class such as aryl phosphates.

- Thirdly, many existing tests have not been designed for efficient use on a broad scale, so they require systematic development.

Development of test standards, a statutory requirement under TSCA for rule-making, will be the culmination of an evaluative-research process; our success in this effort will rely a great deal on the personnel in ORD laboratories and their research. In summary, the regulatory needs of OTE can be stated as: expansion of the data base on screening tests of general and specific function to facilitate the empirical determination of which tests and parameters to standardize; the determination of relative specificity, sensitivity, and utility of tests in different disciplines; and the refinement of the broad array of existing neuropharmacological tests for use in neurotoxicological testing.

2. Research Strategy

The area of neurotoxicology is very appropriate to illustrate the problems encountered in evaluating target organ toxicity. The incredible complexity of the nervous system has become in a sense a cliche, but it is also a fact. Owing to this complexity, it is extremely difficult to perform simple evaluations of toxicant-induced changes in nervous system function. The broad range of approaches which have historically been utilized in neurobiology, from morphology and biochemistry to behavioral analysis, must also be incorporated into the development of neurotoxicological test methods. Otherwise the efficiency of any screening method to detect damage simply cannot be evaluated.

By incorporating multi-disciplinary testing into the tier structure, we can maximize the likelihood that neurotoxicity will be detected, characterized, and quantified. At the first level of testing, the screening level, toxicant-induced neurobehavioral alterations will be the primary test methods. At the second level, the evaluation level, testing will determine the exact nature of this toxicity and will more thoroughly define dose-response relationships which are essential for risk assessment.

To be useful for screening, a test must be sensitive, reliable with respect to a minimum of false negatives, and cost-effective. Recently, considerable attention has focused on the use of locomotor activity as a primary screen. This test has a demonstrated sensitivity to a variety of substances including pesticides, heavy metals, solvents, and psychoactive drugs. However, a number of factors influence locomotor activity levels as well as chemically-induced changes in these levels. This is also true for most neurobehavioral measures, and therefore, consideration is being given to defining more clearly the organismic and environmental factors which influence these measurements. Data are being collected using both acute and subacute exposure to a variety of neurotoxicants. In addition to measures of locomotor activity, other neurobehavioral indices being evaluated as primary tests include measures of acquired behavior learning, memory, and performance), neurophysiology (evoked and spontaneous electrical activity), and neurochemistry (neurotransmitters and neuroenergetics).

Once neurotoxicity is indicated, testing is needed to: (1) rule out false positives in the screening level, and (2) more extensively define this toxicity in both a quantitative and qualitative manner. Therefore, specific functional tests are being evaluated for their reliability and sensitivity at the second and third levels of testing. Tests currently being investigated in the Agency include: measurements of learning and memory (using visual discrimination-taste preferences, spatial alternation, and spatial memory); performance acquisition (utilizing operant techniques under a variety of schedule control conditions); neuromotor function tests (including locomotor patterns such as gait andd stride); social behavior (including sexual and aggressive behaviors); neurophysiological techniques (including sensory evoked potentials, nerve condition, velocity, and both chemically- and electrically-induced seizure patterns); sensory motor function (as measured by optokinetic nystagmus); and neurochemical parameters (including measurements of specific enzymes, neurotransmitter substances, and neuroenergetics).

With few exceptions, the neurobehavioral programs described have also been applied to the developing organism. The importance of these studies derives from the fact that perinatal exposure to toxic substances is widespread in our society, and that in many instances the developing nervous system is especially vulnerable to the deleterious effects of chemicals. Developmental neurotoxicology studies (behavioral teratology) with rodent models have also included postnatal exposures because of the extensive development the central nervous system undergoes during this period. There are many unique methodological problems associated with this area of research, i.e. the need for "between groups" comparisons, longitudinal testing, etc., which are currently being addressed in the neurotoxicology program.

The initial efforts in the neurotoxicological program are aimed at evaluating such specific chemicals as methylmercury, various alkyl tin compounds, and a variety of insecticides and rodenticides because of their known or suspected neurotoxic properties. These compounds are suitable for initial studies which will allow exploration of the relationships between acute, subchronic, and chronic exposures. These initial studies should also provide information on the specific neurobehavioral alterations and the general means by which dose-response data may be used for risk extrapolation to humans. The neurotoxicology research effort will concentrate on implementing the most promising test methods to gather sufficient data for assessing their relative utility and sensitivity and ultimately for selecting those tests which are most appropriate to the regulatory settings.

3. Research Program

Code #		Immediate Research Goals	OPTS Priority
C-1	●	Select and validate the best means of assessing locomotor activity.	1
C-2	●	Develop and validate tests suitable for incorporation into a functional observational (or minimally equipment-dependent) test battery; (e.g. seizure thresholds, motor tests of stride and gait, and acoustic startle reflex).	1
C-3	●	Develop and validate tests suitable for assessment of specific functions and comparison of alternative techniques for similar functions (e.g. rapid training and testing methods for operant conditioning studies of cognitive and discriminative functions, and comparison of visual evoked response to visual discrimination performance).	1
C-4	●	Develop and validate the same kinds of tests and special tests for perinatally exposed organisms.	1
		Intermediate Research Goals	
C-5	●	Evaluate and implement procedure to measure alterations in specific behaviors as indicators of exposure and of potential toxic effects in man.	3
C-6	●	Correlate sexual dimorphic behavior with the reproductive development effects of toxic substances on the development of social behavior in rodents.	3
C-7	●	Evaluate a series of electrophysiological procedures (i.e. EEG, evoked potentials, etc.) as indicators of neurotoxicity.	2
C-8	●	Develop more quantifiable and less subjective means of evaluating neuropathological lesions, including automated morphometric analysis techniques.	3

C-9	●	Develop and validate screening tests for neuroenergetics and the correlation of neurochemical with functional data.	3
C-10	●	Develop biochemical indicators of neurotoxic responses.	3
C-11	●	Assess the validity and usefulness of tests for sensory-motor function (Optokinetic Nystagmus).	3
C-12	●	Evaluate macroelectrode neurophysiological techniques.	3
C-13	●	Evaluate effects of toxicant exposure on tests of specific temporal response patterns, learning, and sensory discrimination in animals.	2
C-14	●	Evaluate olfactory effects of airborne toxicants.	3

Long-Range Goals and Basic Research

C-15	●	Develop an EPA laboratory capibility to execute the OTE Tier Testing Program when needed by the Agency.	4
C-16	●	Develop class-specific (e.g. chlorinated solvents) comprehensive test programs utilizing multi-disciplinary teams of neuroscientists.	4
C-17	●	Develop toxicological support for neurotoxicological testing (e.g. inhalation exposure facilities).	4

D. MUTAGENICITY TESTING

1. Background and Status

The primary objective of mutagenicity testing is to determine the potential of a chemical agent to induce mutations in humans. Quantitative assessment of this potential genetic risk is an ultimate objective of a regulatory agency concerned with controlling mutagens in the environment. Health related endpoints which are of interest in genetic toxicology are point (gene) mutation and chromosomal alterations.

Point mutations are alterations which affect single genes. These alterations include base pair substitutions and frameshift mutations, as well as other small deletions and insertions. Existing *in vitro* test systems include both forward and reverse mutation assays in bacteria, yeast, fungi, and mammalian cells in culture. The prokaryotic (e.g. bacterial systems detect only point mutation, whereas eukaryotic systems detect both point mutation and chromosomal alterations. Also, most *in vitro* assays must employ an exogenous source of metabolic activation in the form of a mammalian liver microsomal preparation. The majority of genetic toxicants must be converted into reactive forms before their effects can be detected. This metabolic conversion is thought to be mediated by oxidative enzymes and to involve the formation of electrophilic metabolities which bind covalently to DNA.

Short-term *in vitro* assays for gene mutations include tests in insects, plants, and intact animals. The sex-linked recessive lethal test in the fruit fly *Drosophila melanogaster* has been the most widely used *in vivo* gene mutation assay to the present time. However, higher plants offer special advantages as *in situ* monitoring systems, which may be of particular utility in environmental studies.

Chromosomal alterations include the loss or gain of entire chromosomes, chromosome breaks, non-disjunctions, and translocations.

Tests for these abnormalities involve searching for chromosomal aberrations in somatic and germinal cells usually obtained from insects and mammals. Chromosomal aberrations observed in the germinal tissues of mammals provide important evidence of the accessibility of the test chemical to the reproductive organs. Thus, positive evidence of specific gene mutation seen in *in vitro* tests, along with observations of chemically-induced chromosomal damage in germinal tissues of rodents, suggests that the chemical under evaluation has the potential to produce heritable effects.

DNA damage and repair bioassays do not measure mutation *per se*, but do measure direct damage to DNA and other macromolecules by chemical agents and the subsequent repair of that damage. Bioassays to detect macromolecular damage and repair are available using bacteria, yeast, mammalian cells, and whole animals.

The present tier schemes for mutagenicity are divided into two parts: a scheme for the detection of gene (point) mutations and a scheme for the identification of chromosomal mutations.

Both schemes are directed toward an estimation of risk to man from a potential mutation. To assess risk, it must be shown that the suspect chemical reaches the germ cells and that once there it interacts with DNA to cause a heritable mutation. Both tier schemes have three levels: Level I -- Identification; Level II -- Confirmation; and Level III -- Risk Assessment.

In the tier scheme for gene mutations, Level I includes tests for bacterial mutations, mutation in mammalian cells in culture, and DNA damage and repair. Confirmatory assays include sex-linked recessive lethal tests in *Drosophila melanogaster*, and under the appropriate circumstances, tests for point mutation in mammalian cells in culture. Level III includes the mouse specific locus test, a test for sperm alkylation in mice, *Drosophila*, and mammalian cells in culture.

To date, the proposed tier schemes have not called for a mouse specific locus test as a basis for risk estimation. Rather they have relied upon molecular dosimetry as a bridge between mammalian germ cell involvement (as evidenced by mouse sperm alkylation) and mutational dose response as determined in *Drosophila* or mammalian cells in culture.

2. Research Strategy

The mutagenesis research strategy plan will focus on: (1) the development and validation of systems for detection and confirmation of potential mutagenicity, especially those tests which will demonstrate the mutagenicity of a chemical in human and animal germinal tissues; (2) the continuation of longer-range research programs which provide a firm base from which new bioassays in genetic toxicology can be developed for aneuploidy detection and risk assessment; and (3) the establishment of a major effort in the development, use, application, and interpretation of hazard assessment methodology in the regulatory process.

The use of tier testing schemes to identify and quantitate the hazard due to environmental mutagens for regulatory purposes has placed great emphasis on existing state-of-the-art methodology in this field. Unfortunately, bioassay systems which were originally designed for mechanistic and exploratory research have been placed in the regulatory process without much regard for system design, applicability, validity, and availability. To meet regulatory needs, existing test systems need to be redefined and realigned so that the desirable characteristics of reproducibility, high sensitivity, specificity, and ease of performance can be acquired.

The ideal tier scheme requires a lower tier which is sensitive and which does not generate false negative results. First level tests for mutagenicity can include bacterial mutation bioassays, mammalian cell mutation bioassays, DNA damage and repair bioassays, and *in vitro* and *in vivo* cytogenetics bioassays. Second level tests which confirm mutagenic activity for gene mutation can include the sex-linked recessive lethal in *Drosophila*; those for chromosomal aberration can use the mouse dominant lethal. Third level tests which provide data for quantitative risk assessment can use the mouse specific locus and germinal dosimetry or mouse heritable translocation bioassays for gene mutations and chromosomal aberrations respectively.

The research emphasis will be in the development of improved methods for all three levels of testing and will be concerned with the development of test systems which detect endpoints, such as aneuploidy, for which there are no bioassays available. The improvement of existing bioassays to increase their sensitivity and accuracy will also be stressed.

Research in the area of hazard assessment will be directed at risk estimation by application of existing bioassays, by the modification of these bioassays to give highly reproducible and accurate data, and by the development of new test methodologies and mathematical models for hazard assessment of mutagens.

3. Research Program

Code #		Immediate Research Goals	OPTS Priority
D-1	●	Develop methodologies to detect mutagens in germinal tissue under the conditions of environmental exposure	1
D-2	●	Develop methods for testing volatile substances in *in vitro* test systems.	3
D-3	●	Validate the YFF sperm morphology test to monitor human exposure.	4
D-4	●	Validate the microlesion assay for gene mutations.	2
D-5	●	Develop criteria for determination of what constitutes a positive or negative test result in mutagenicity assays.	2
D-6	●	Develop statistical models for test evaluation.	2
D-7	●	Conceptualize and develop a program to assure quality of regulatory data obtained under TSCA.	2
		Intermediate Research Goals	
D-8	●	Expand the data base for all assays to include a wide range of chemicals that can be used for validation of each system.	3

D-9	●	Develop more sensitive and alternative indicators of gene mutation, chromosome breaks, rearrangement, and non-disjunction, especially for tests relating to hazard assessment.	3
D-10	●	Expand the data base on the mouse specific locus test by testing individual chemicals.	2

Long-Range Goals and Basic Research

D-11	●	Determine the cost of genetic defects in the human population.	1
D-12	●	Develop mathematical models for risk assessment.	1
D-13	●	Improve test methods and standardize procedures for assays in all levels of the mutation scheme.	4
D-14	●	Improve activation systems for all *in vitro* assays.	3
D-15	●	Develop *in vitro* human cell lines for gene mutation, DNA damage and repair, and *in vitro* cytogenetics.	3
D-16	●	Develop markers of any kind for specific locus and translocation assays.	2
D-17	●	Conduct research on mutagenesis assays with female animals.	2
D-18	●	Determine alkylation in sperm DNA as an indicator of genetic hazard.	1
D-19	●	Determine the dominance of non-sex-linked traits.	2
D-20	●	Develop biochemical methods for monitoring the human population for exposure to mutagenic agents (e.g. circulating RBC, HGPRT mutants, alkylated hemoglobin, immunologic techniques for mutagen-DNA adducts).	1
D-21	●	Examine the genetic basis of gene mutation at the thymidine kinase and ouabain loci.	2

D-22 ● Develop appropriate bioassay for aneuploidy. 2

E. CARCINOGENICITY TESTING

1. Background and Status

Cancer is the second leading cause of death in the United States, resulting in the death of one out of every five Americans. Thousands of new chemicals are introduced yearly into the environment that have the potential of greatly increasing the cancer hazard. The prudent way to reduce the cancer risk to humans would be to identify environmental carcinogens so that they can be removed from use and to screen new chemicals for carcinogenic potential prior to their introduction into the environment.

Environmental chemicals can affect human cancer rates by several distinct mechanisms. Chemicals may act as tumor initiators, promotors, or carcinogens. Tumor initiators are capable of producing a change in the genotype of cells which can be irreversible and can eventually progress to a tumor. The ability to initiate tumors has been closely associated with somatic mutation, allowing the use of simple *in vitro* and bacterial systems as a qualitative means of detecting tumorigenic chemicals. Tumor promoters act subsequent to the initiating carcinogen to decrease the latent period of tumor development, and/or lead to higher incidences of cancer. Tumor promoters have been identified in humans and laboratory animals for almost all organs and tissues including the skin, liver, colon, bladder, lung, and mammary gland. Chemicals which are capable of both tumor initiation and promotion are referred to as complete carcinogens. Modifiers of the carcinogen progression that act during the initiation stage (i.e. when the carcinogen is administered) are called cocarcinogens. Fluoranthrene, the most abundant environmental polycyclic aromatic hydrocarbon, is the prototype cocarcinogen. Tumor promoters and cocarcinogens represent a health hazard since they can increase both chemical-induced and viral-induced tumors and the rate of "spontaneous" malignancies.

Epidemiological studies have associated a limited number of chemicals with human cancer. However, it is infeasible to rely on epidemiological studies for the determination of the carcinogenic potency of new chemicals because of the 15- to 30-year delay in the appearance of most tumors after the exposure of humans to a carcinogen. Regulation of new chemicals for carcinogenicity will have to be made on animal bioassays instead of waiting for people to be exposed for many decades. Many environmental carcinogens and promoters have been identified in laboratory animals. Because of the similarity of the carcinogenic progression in man and animals, it is reasonable to assume that at least some of those animal carcinogens are also human carcinogens. All human carcinogens except arsenite have been shown to be animal carcinogens. The extrapolation of the animal carcinogenicity data to man is required for a risk-benefit analysis.

In order to provide a consistent, cost-effective approach to testing and evaluation of data for the purposes of TSCA, it is necessary to develop and validate those tests which are reasonable predictors of oncogenicity in humans and to place them in the most appropriate positions in a testing and evaluation scheme. The scheme will help determine the weight of different types of evidence EPA will receive and help provide a sound approach to the evaluation of that evidence.

In the tier scheme, the first group of tests (initial biological tests) presently includes mutagenicity assays such as the Ames test and mammalian cell tests, DNA damage and repair assays, and *in vivo* and *in vitro* cytogenetics. These tests mainly detect a chemical's ability to interact with DNA in the cell. Ongoing research on these tests includes validation of predictors of oncogenicity, development of consistent guidelines for assessment of results, and improvement of current tests and/or development of new tests that do not overlap the effectiveness of the current ones. At this level, false negatives should be kept at a minimum. As a result, a number of false positives will sift through to the next group of tests.

The second group of tests (confirmatory biological tests) contains additional *in vitro* or *in vivo* assays which will confirm the results of the previous tests. These tests' results tend to be more accurately extrapolated to the human situation. Thus, most of these tests involve the use of whole animals. It is important here to have a low level of false positives. The tests that are currently being considered for this group are *in vitro* cell transformation studies, a lung adenoma bioassay, a skin painting bioassay, a mammary carcinogen bioassay, and the liver microfoci bioassay. All of these tests need further validation and improvement in order to eliminate the high incidence of false negatives in some of them.

The third group of tests is the most relevant to the human situation. These tests are whole animal studies and are of longer duration (normally at least 2 years in a rodent study) than the previous two groups. They give more credible results in terms of oncogenic potential and are usually considered by EPA to be substantial evidence. When coupled with positive epidemiological results, a positive 2-year animal bioassay is considered by EPA to be the best evidence possible.

Presently, the primary goal for the completion of the oncogenicity testing and evaluation scheme is the validation of the tests mentioned above as predictors of oncogenicity in humans. This will involve an immediate and extensive investigation and evaluation of the literature. The secondary goal is to develop and evaluate methods for detecting promoters and cocarcinogens. The present scheme does not take these into account. These methods should follow a basic scheme similar to the one outlined above.

2. Research Strategy

It has been proposed that chemical carcinogens initiate carcinogenesis by altering DNA, which results in somatic mutations and chromosomal aberrations. The similarity in the mechanism of mutagenesis in prokaryotes and eukaryotes has permitted the use of rapid and inexpensive bacterial and other in vitro systems to screen for mutagens. The first level of testing in the carcinogenesis area utilizes the same bioassays used in the mutagenesis area as a result of a close relationship between chemicals which induce cancer and those producing mutations in lower animals. The primary requirement at this level of testing is that false negatives be kept at a minimum. Consequently, redundant tests must be eliminated from this level in order to maintain the cost-effectiveness.

The non-carcinogenic mutagens and clastogens can be operational false positives, so they should be eliminated from the decision tree by a set of second level bioassays. Implicit in target organ susceptibility to particular carcinogens is that there is a condition for carcinogenesis beyond the initial biochemical lesion presumed to involve DNA. Numerous chemicals lacking carcinogenic potency bind and damage the DNA of a given organ to extents greater than carcinogens. The properties that distinguish carcinogens from other DNA-altering chemicals are those which can discriminate between carcinogenic positives and false positives observed at the lower level of testing.

False positives in the first testing level can result from any pharmacokinetic or metabolic factors not taken into account in lower level test systems. Chemicals giving false positives might not be systemically absorbed and metabolized in intact animals, rendering lower level test results irrelevant. The differences in metabolism need not be qualitative. Quantitative differences can be such, that in the higher order tests, the amount of the biochemical lesion that initiates the carcinogenic process is low enough to be repaired. Other mechanisms by which false positives would be detected in first level tests are differences in the rates of detoxification of the chemical and/or the repair of the biochemical lesion of initiation.

A research strategy to establish second level test methods requires the development of target organ bioassays that are sensitive to carcinogens of all chemical types and that take into account factors such as differences in pharmacokinetics. Prime candidates for this level of testing are the short-term bioassays that employ benign lesions as a determinant of carcinogenesis and tumor promoters to decrease the latency. The spectrum of chemicals to which each test is sensitive must be determined in order to insure an acceptable level of false negatives without redundancy. Quantitative relationships that might exist between the results of these short-term bioassays and Level III lifetime exposure should be determined.

Other second level tests available are those which measure the malignant transformation of rodent or human cells in culture. These oncogenic transformation bioassays are rapid, relatively low in cost compared to in vivo tests, and have been able to detect a wide variety of classes of chemical carcinogens. Cells which have been transformed in culture will grow unhindered when implanted into animals, and thus the test measures true malignancy. Some types of oncogenic transformation tests give quantitative dose-response information; however, it is not clear that these results reflect in vivo potency. The disadvantages of these tests are limited activation systems, omission of pharmacokinetic considerations, lack of standardization, and incapability of quantitative reproducibility.

Third level bioassays involve chronic exposure of a chemical to intact animals with extensive pathological examination to detect the occurrence and onset of tumors. Usually, testing is done in two species by the route of major exposure in humans. The ultimate assay is expensive, takes approximately 3 years for completion, and requires elaborate animal facilities and highly trained professionals. Both facilities and trained personnel are in limited supply. The established correlation of the third level bioassay with human epidemiology must remain the basis for carcinogenesis risk assessment.

It is important to realize that the testing strategies outlined above and those currently in use primarily address the initiation of tumors. It is the policy of EPA to consider that tumor promotors are carcinogens. Therefore, the synthesis of tests to detect promotors and cocarcinogens into the current tiered testing scheme is essential to assess carcinogenic risk. Research into the essential characteristics of promotors must be performed. The observed actions of promotors, such as DNA replication, cell division, and hyperplasia should be explored. Research to determine the mechanism underlying tumor promotion is necessary for the development of short-term and inexpensive Level I bioassays.

The process of tumor promotion is reversible and in laboratory animals would appear to have a threshold dose of no effect. The extrapolation of the animal data to humans, however, requires the development of models. These models will have to be validated with epidemiological evidences of tumor promotors. Therefore, a major research effort is required in the determination of the dose-response relationship of tumor promotors in animals and in the epidemiological establishment of tumor promotors in man.

3. Research Program

Code #		Immediate Research Goals	OPTS Priority
E-1	●	Establish a matrix for oncogenicity bioassays at Level II.	1
E-2	●	Establish the level of confidence in the matrix by systematic testing with known carcinogens of different class and target organ specificity (test systems in the matrix to include, among others, systems indicated below).	2
E-3	●	Develop and validate the SENCAR mouse as a Level II bioassay, defining its responsiveness to chemicals applied topically, parentally, and orally.	1
E-4	●	Document the influence of different experimental procedures possible in the liver microfoci assay on the response to known chemical carcinogens.	1
E-5	●	Test the strain A mouse as a Level II assay using multiple routes of exposure (i.e. intraperitoneal, oral, and inhalation).	1
E-6	●	Evaluate the mammary gland carcinoma bioassay as a Level II oncogenic test system.	1
E-7	●	Evaluate the available in vivo molecular markers for tumor promotors and develop new ones if current ones prove unsatisfactory.	3
E-8	●	Investigate the utility of using unscheduled DNA synthesis as a means of detecting compounds poorly detected by current Level I bioassays.	5
E-9	●	Develop and evaluate in vitro tests for tumor promotors.	4

E-10	●	Negotiate with the NCINTP carcinogenesis bioassay program to include archetypal chemicals in long-term assays to better establish carcinogenic potencies.	4

Intermediate Research Goals

E-11	●	Assess the ability of measures of DNA damage (alkaline-labile sites, endonuclease recognized damage, etc.) produced by a chemical *in vivo* to predict its carcinogenic potency.	4
E-12	●	Determine if a matrix of short-term *in vivo* bioassays can be used as a surrogate for the much more expensive and time consuming lifetime carcinogenesis bioassays.	3
E-13	●	Correlate the response of *in vivo* molecular markers of tumor promotion in various organs with tumor promoting activity of chemicals in target organs.	2
E-14	●	Improve the methods for metabolic activation, reproducibility of results, sensitivity of systems, and methods for data analysis of oncogenic transformation assays.	2
E-15	●	Determine if *in vivo* unscheduled DNA synthesis can serve as an indicator of carcinogenic potency.	3

Long-Range Goals and Basic Research

E-16	●	Conduct research to elucidate the mechanism(s) involved in tumor promotion of different target organs.	5
E-17	●	Define mechanisms which operate in cocarcinogenesis with the aim of establishing short-term bioassays for these phenomena.	5

F. METABOLISM

1. Background and Status

Metabolism of toxic chemicals here refers collectively to the processes of absorption, distribution, metabolic alteration, and excretion of chemicals from the body. One of the basic principles of toxicology is that the processes by which chemicals are handled metabolically greatly influence both the quantitative and qualitative characteristics of a chemical's toxic effects. Although standards cannot be established based on metabolic data, metabolic data can provide critical information in three areas:

- Where conflicting data exist concerning the toxicity of several species, metabolic data may be able to establish the species most proximate to man. This presumes that the metabolism of the compound is known.
- Metabolic interactions are often involved in synergisms and antagonisms.
- The generation of certain electrophilic intermediates capable of entering into covalent interactions with DNA can serve as presumptive evidence of carcinogenic or mutagenic activity at the first level of testing.

The metabolism of toxic chemicals represents only one possible basis for interspecies differences in response to toxic chemicals. In the case of chemical carcinogens and mutagens, the biological response can vary according to the ability to repair DNA damage induced by the chemical and the presence or absence of exogenous or dietary promoting agents. Genetic factors in xenobiotic metabolism also indicate differences in the intrinsic sensitivity of a species to these chemicals. Similarly, species variability in teratogenic responses is sometimes traceable to differences in placental type and function. Consequently, it is essential that any research directed at species differences in response to toxic chemicals include studies of intrinsic sensitivity as well as xenobiotic metabolism.

2. Research Strategy

In only very special circumstances would it be likely that a chemical would be regulated solely on the basis of metabolic data. Thus it is essential that the metabolism of toxic chemicals be studied in the same context as the toxicity of a compound. Nevertheless, it is likely that the success of regulatory actions on specific chemicals will increasingly involve consideration of a chemical's metabolism. In fact, the principal substantive challenges in the recently proposed water quality criteria have been based on interspecies differences in the metabolism of chemicals. The principal difficulty involved in accepting such arguments is simply the absence of comparable data in humans. Consequently, the general approach has been to accept the premise that the most sensitive species tested best represents man.

To accommodate the diverse need for metabolic data, the adoption of a two-fold strategy is suggested; one approach applied, the second somewhat more basic or anticipatory. The applied approach is taken in the course of studying any toxicological endpoint in which metabolism is a likely basis for interspecies response differences. Documenting differences in metabolism should be either an integral part of the experiments or performed in retrospect as a means of establishing whether metabolic differences are responsible. It is only by meticulous study of individual cases that a sufficient data base can be established to allow generalizations concerning what the most appropriate data might be.

A more basic program in metabolism, however, is necessary for the Agency to remain in an authoritative position in future regulatory activities. Industry is making considerable investment in the area of comparative metabolism. To establish an Agency capability to evaluate the significance of metabolic differences accounting for species differences in toxicity, a base program needs to be established. The key problem that must be considered in establishing such a program is that without some means of studying metabolism in man, the utility of the results will be virtually nil. The program planned will essentially pursue two questions:

- Does metabolism of foreign compounds by cells in organ or cell culture accurately reflect metabolism *in vivo* in commonly employed laboratory animals?
- If the first point can be established, can the comparison of a chemical's metabolism in human organ or cell culture vs. that in cultures derived from experimental animals provide the means whereby meaningful across-species comparisons can be made?

The main value of this effort will be realized as data are obtained from these essentially separate efforts. Comparison of across-species differences in sensitivity to particular toxic effects with comparative metabolic work will establish the data bank upon which predictions can be made concerning the relative importance metabolism plays in a chemical's toxicity. This data bank will be based on experience with related compounds and a basic knowledge of the metabolic pathways involved.

Throughout this effort, however, it should be kept in mind that metabolic differences between species must be considered in relation to other factors which can account for differences in a toxic effect between species. When metabolism cannot be shown responsible for such differences, active pursuit of alternative factors is essential to put across-species toxicological response variation in proper perspective.

3. Research Program

Code #		Immediate Research Goals	OPTS Priority
F-1	●	Investigate the ability of pharmacokinetic models to account for across-species differences in sensitivity.	1
F-2	●	Develop predictive models for comparing the impact of differing routes of exposure based upon physical-chemical characteristics and structural analogs.	3
F-3	●	Develop systems for interspecies extrapolation of metabolism/pharmacokinetics data.	1
F-4	●	Determine whether covalent binding of electrophilic intermediates to proteins and/or nucleic acids in critical organs can be correlated with chronic toxicity, carcinogenesis, and teratogenesis.	1
F-5	●	Develop predictive models for the pharmacokinetic and metabolic characteristics of different placental types. Determine to what extent data can account for across-species differences in teratogenic responses.	2
F-6	●	Determine the extent to which DNA damage induced by chemical carcinogens can be correlated with carcinogenic responses in target organs.	2

Intermediate Research Goals

F-7	●	Develop in vivo integrating dosimeters for chemicals which are reactive or metabolized to reactive intermediates (carcinogens and mutagens), and which are suitable for use as a means of correcting for across-species differences in pharmacokinetics and metabolism.	1

Long-Range Goals and Basic Research

F-8	●	Determine specific carcinogen-DNA adduct and nonspecific DNA damage occurrence in human lymphocytes using radio-immunoassay techniques.	4
F-9	●	Determine if primary cell and/or organ cultures from different species accurately represent the metabolic and damage and repair characteristics of the tissue in vivo.	3
F-10	●	Determine the relative reactivity and stability of reactive metabolic intermediates.	1
F-11	●	Determine the transport mechanisms by which reactive intermediates reach sites of attack.	2
F-12	●	Determine the metabolism in specific organs and tissues to clarify expressions of toxic effects.	2
F-13	●	Establish a data bank of chemical interactions analogous to drug interactions.	2

G. EPIDEMIOLOGY

1. Background and Status

Epidemiology atempts to explain disease causation by examining the distribution and determinants of disease in human populations. In contrast to usual toxicology approaches, epidemiology is opportunistic in nature, utilizing existing human exposure situations to gather health data. When dealing with chemical agents causing irreversible effects, such as teratogens, mutagens, and carcinogens, any experimental approach to study humans is precluded and available human studies are limited to existing circumstances. This does not imply that sound epidemiology studies are not feasible. However, it does mean that only selected chemical compounds will be amenable to study since the exposed group must meet requirements of adequate size and duration and level of exposure. Epidemiology studies will therefore be complimentary to toxicology testing, conducted in parallel, and will provide a general data base for extrapolation from animals to humans.

In this context, epidemiology assumes a vital role; only through this approach can animal testing systems be validated to determine how accurately they qualitatively and quantitatively resemble man in their biological response.

The relationship of man-made chemicals in the environment to human morbidity and mortality is essentially unknown at the present time. Relatively few epidemiologic investigations have been conducted to test the hypothesis that environmental chemicals contribute significantly to human disease. Studies that have been carried out have been generally either purely descriptive or ecologic in design. In an ecological approach, the unit of exposure and analysis is the group rather than the individual. Such studies can provide evidence of increased risk; however, a quantitative risk estimate is usually best derived from more sophisticated studies which are organized on an individual basis and utilize case-control or cohort designs. Some form of cohort design is usually best suited if the focus is directed towards a specific chemical exposure and if an identified exposed group is available. In a cohort design, the population at risk is followed through time, either retrospectively in an historical cohort analysis or prospectively. The incidence of particular pathologic conditions is determined, and disease rates are compared between exposure groups to develop dose-response relationships or are compared to other standard populations. This approach has been used widely in occupational settings to quantify human carcinogenic risk.

If a particular disease rather than an exposed population is the orientation, a case-control design is usually more appropriate. Cases with a specified pathologic condition are matched with suitable controls and individuals are then studied to determine the occurrence of the primary hypothesized risk factor and other known risk factors in both groups. Relative risks are calculated to determine if an association is present.

Since epidemiology is a methodology, its categorical placement in a tiered testing scheme is not practical. The following justifications support this consensus: the long duration and uncertain outcomes of feasibility studies; the long duration of epidemiologic studies; the possibility that relevant health effects may be overlooked; and the detection capabilities of studies may be limited by known biological endpoints. As a result of the inability to incorporate directly epidemiologic studies in a tiered system, several alternative roles are being considered. These roles, which are outlined below, include ad hoc/specific uses, use for information gathering with Sections 8(a) and 4(a) of TSCA, generic epidemiologic screening, and proportionate mortality or morbidity.

- Ad Hoc/Specific Uses - There may be specific situations in which analytical epidemiologic studies would be highly useful and practical, or in which TSCA's Section 4 authority could enable EPA or some other party to initiate or complete a planned or ongoing study. Such studies will be conducted on an ad hoc basis, rather than being triggered within the tier system.

- Information Gathering with TSCA's Sections 8(a) and 4(a) - Under Section 8(a), EPA may obtain a wide range of existing data and information from the files of chemical manufacturers and processors (e.g. exposure monitoring and medical record systems). The development of an 9(a) rule specifically for epidemiology is being considered. Section 4(a) may be used to obtain new data or data which are not "reasonably ascertainable" from industry files. Section 4(a) and 8(a) information may be useful in determining the feasibility of epidemiologic studies, which may be conducted on an ad hoc basis, as previously described.

- Generic Epidemiological Screening - Information obtained through screening populations under Section 4 authority may supply Level I suggestive information and be useful in analytical studies conducted either by EPA or other organizations. A battery of suitable human effect indicators should be developed for each health effect area.

- Proportionate Mortality or Morbidity Ratio (PMR) Analyses - PMR analyses, which may be conducted quickly and at small expense, may be useful in supplying Level I type information. In a PMR analysis, the fraction of deaths or cause of disease over all deaths or illnesses in a study population is compared to the fraction in a standard population. PMR analyses may give misleading results since this calculation does not deal with rates. It is, however, relatively easy to conduct by utilizing data from such sources as medical and death records. The feasibility of requiring industry to conduct such studies is being investigated. The usefulness of such studies in general is also being assessed through a literature review.

2. Research Strategy

Epidemiology has several roles in chemical testing and assessment. The first study types to be considered are descriptive or ecologic investigations, generally categorized as hypothesis generating studies. These studies are important because they are often a logical first approach to identify problems, because they provide impetus and information for designing more specific analytic investigations, and because they tend to be quick and relatively inexpensive. In this category are descriptive studies such as cancer mapping, international disease comparisons, and other broad ecologic designs. The information obtained tends to be suggestive evidence rather than strongly conclusive, thus when circumstances allow, more definitive studies would be conducted to follow up the results.

Hypothesis testing investigations include analytic epidemiologic studies in which a quantitative risk estimate is derived. The methodologies employed include the standard case-control, cohort, and cross-sectional designs. Data are collected usually on an individual basis, and all known potentially confounding variables are accounted for to the extent possible. Dose-response relationships are pursued whenever feasible since they often provide the strongest etiologic evidence.

These types of investigations are commonly utilized in occupational settings, but they have been applied much less frequently to environmental exposures of the general community. These studies serve the dual purpose of establishing effects of specific chemicals on humans and providing the data base for validating toxicological models.

Methodology development is an important area where additional epidemiological research is needed. Although new designs and analytical techniques are a consideration, the emphasis in this area will be directed towards (1) developing more sensitive and accurate measures of pathologic damage than can be applied to population studies, and (2) applying proven epidemiologic methods to new situations. An example of the latter would be the adaptation of historical cohort designs (commonly used in occupational studies) to the general community. Such an application could provide direct risk estimates for the general population.

Epidemiologic support of toxicologic dose monitoring techniques is necessary to confirm methods developed to measure doses of toxins, particularly carcinogens, in human populations. After refinement of the methods in animal experiments, exposed human populations would be sampled to validate the technique. The ultimate objective is to develop the capability for screening exposed groups to identify high risk groups and to quantitate dose in epidemiologic investigations.

3. Research Program

Code #	Immediate Research Goals	OPTS Priority
G-1	● Determine the usefulness of proportionate mortality or morbidity analyses as an initial screen for health effects.	2
G-2	● Conduct analytical epidemiological studies of adverse health effects to estimate human risks.	1
	Intermediate Research Goals	
G-3	● Develop more accurate and sensitive indicators of pathologic changes that can be feasibly applied in epidemiologic studies. Refine selected clinical laboratory testing methods to better quantitate interpretation of results that might indicate mild functional impairments due to chronic low-dose exposures.	3
G-4	● Conduct studies to determine the adverse effects of chemical compounds on the male and female reproductive system. In the male, effects directly on the germ cells will be studied through semen analysis. Toxicity to the female and embryo will be studied through reproductive outcomes, spontaneous abortion, and congenital malformation. Fertility is a major concern.	2
G-5	● Improve the statistical techniques used in epidemiology. Examples: -- Refine statistical tests used to obtain confidence limits on relative risks from paired case-control studies. -- Compare available techniques for taking into account characteristics of a population which may not be balanced between cases and controls. Determine which of the techniques are best or develop new methods for adjusting for these characteristics.	3

G-6	●	Conduct epidemiologic research to determine the impact of specific chemical compounds in the environment on general community morbidity and mortality. Both broad spectrum ecologic studies and specific analytic investigations are needed. New applications of methodologic approaches such as the higtorical cohort design to new situations, such as the general community population, might enable more precise quantification of risk to the community from low level exposures.	3
G-7	●	Conduct studies of known high risk groups to determine if certain diseases that appear environmentally-related are associated with specific toxic exposures.	1
G-8	●	Validate toxicologic dose monitoring techniques in human populations.	4

Long-Range and Basic Research Goals

G-9	●	Improve and attempt to standardize the study techniques used in epidemiologic research. Examples: -- Establish standards for selective appropriate methodologies to be utilized. For example, examine the usefulness of case-control studies within a cohort design. -- Develop better capabilities for controlling confounding variables through study design.	3

III. CHEMICAL SPECIFIC CONCERNS

A. EVALUATION OF ASBESTOS AND ASBESTOS-LIKE MINERALS

1. Background and Status

Asbestos is a well known hazard to human health, and the Agency is actively concerned with controlling its possible environmental impacts.

Asbestos-like minerals are commonly found in large areas of American bedrocks (Figure 4-1). Therefore, rock fibers for which the hazards are as yet undetermined are found in many mines and quarries. The existing uncertainty concerning the toxicity of these materials make development of rational regulatory actions impossible. Thus, an understanding of the health effects potential of these minerals and its relationship to their mineralogical characteristics is needed before it can be determined if control measures are needed, and if so, what the design and application of those measures should be.

The development of a safe asbestos substitute, or a means of treating asbestos fibers to render them harmless to man is becoming increasingly important. The only sure means of testing these substitutes is by long-term animal experiments. However, since these tests may take years to complete, shorter-term tests are urgently needed now.

2. Research Strategy

The proposed project for control of asbestos and asbestos-like minerals addresses the following problems:

- Determination of the relative toxicity and carcinogenicity of asbestiform amphibole mineral fibers
- Detection of mineralogical determinants in carcinogenesis
- Development of simpler means of obtaining valid biological parameters
- Application of these principles to the evaluation of real world hazards posed by asbestos and its substitutes and other asbestos-like minerals.

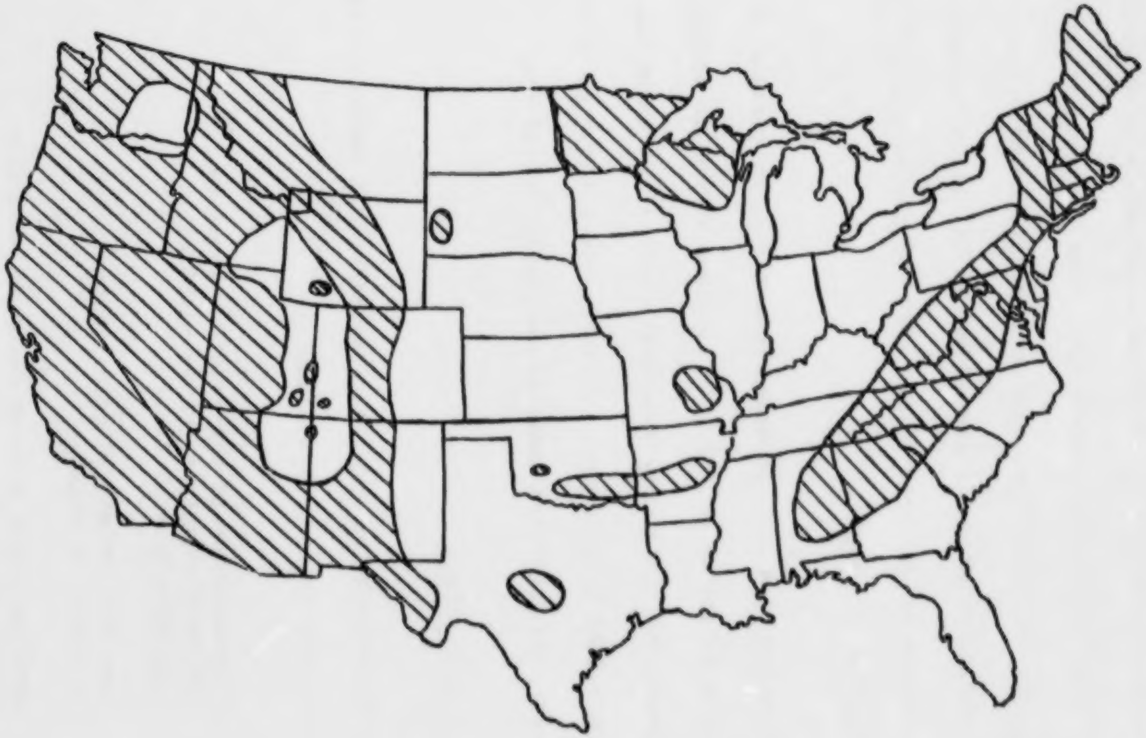


FIGURE 4-1. REGIONS OF THE UNITED STATES (SHADED AREA) REPORTED BY EPA TO CONTAIN ASBESTIFORM MINERALS IN THE BEDROCKS.

Research Program

Immediate Research Goal

- To complete the ongoing *in vivo* and *in vitro* studies of evaluating relative toxicity and tumorogenesis of mineral amphiboles.

Intermediate Research Goal

- To validate the *in vivo* splitting to fibers and correlate the phenomenon with carcinogenesis.

Long-Range and Basic Research Goals

- To develop a short-term system to predict potential toxicity and tumorogenesis of mineral fibers.
- To establish a "representative" sample and establish its toxicity and tumorogenesis as a model for a health and safety evaluation of mixed amphibole mineral fibers.

SECTION 5

ENVIRONMENTAL RESEARCH STRATEGY

I. OVERVIEW

To fulfill the operational dictates of TSCA, test rules and standards, assessment methodologies, and testing schemes regarding the ecological effects and fate of chemicals in the environment must be promulgated. The Office of Testing and Evaluation is responsible for the scientific applications and interpretations that generate these test rules and standards. OTE is supported in this effort by the Office of Environmental Processes and Effects Research (OEPER). Through a comprehensive research and development program, OEPER provides OTE with a scientific foundation for their operations, including the basic science and its applications in test methodologies, interpretative models, and support documentation.

As provided in Section 4 of TSCA, test rules specify the chemicals to be tested as well as the nature and standards of the required tests. The Support Documents for Test Rules should provide an assessment of the environmental fate and effects of the chemical. Thus, a trial assessment of each chemical considered as a candidate for Test Rule promulgation is necessary. This process includes an evaluation of the scientific validity of information sources, an assessment of the potential for environmental impact, and an assessment of the need for further testing to fill in gaps in the information available. Recommended additional testing must provide the necessary information to determine whether or not the suspect chemical would cause an unreasonable environmental impact.

Test standards (or protocols for testing the ecological effects and fate of chemicals) are necessary to implement both Sections 4 and 5 of TSCA. The test standards and the accompanying rationale for the particular test standard (the test standard support document) together provide a guide for new chemical testing (Section 5).

In order to establish a basis for risk assessment and testing decisions, the Office of Pesticides and Toxic Substances has developed an integrated tiered testing and assessment scheme. This testing and assessment scheme will be employed to define the relationships between the various information elements which may be germane to chemical risk assessment. In this capacity, the scheme can be used to help identify potential risks based on analysis of the existing information, as well as to indicate the additional testing necessary for a complete risk assessment.

The testing and assessment schemes for environmental effects will couple information on the production, use, and disposal characteristics of a chemical with data on its physical and chemical properties to formulate a preliminary partitioning analysis. The environmental media and compartments identified in the partitioning analysis will help direct the toxicity testing to appropriate species. Following the partition analysis, an analysis of the chemical's degradation characteristics (e.g. probable persistence in the identified media or compartment) will be performed. This analysis is used to determine whether short-term exposure (acute toxicity tests) or additional long-term exposure (chronic toxicity tests) effects need to be investigated. If the threshold effect levels obtained in the toxicity tests are near the estimated or field-measured environmental concentrations of the chemical, additional chemical fate tests may be needed. In addition, biological uptake analyses may be needed for chemicals which demonstrate chronic toxic effects, or which lead to important non-toxic effects such as flesh tainting.

In summary, the testing and assessment scheme relies on the identification of test data, interpretation of the relationships between effects and environmental concentrations, and the criteria relevant to risk assessment for interpreting the data on the basis of these relationships.

Various means are available to support OTE's operational approach to the implementation of TSCA. Existing information and known relationships provide the primary foundation. New data and new relationships from both the new and already available data (supplied by laboratory and field research) must be obtained. In regard to their role in establishing environmental concentrations of concern (exposure assessment), these data must be organized and interpreted and the value of their relationships documented and validated. The criteria for synthesizing the exposure and hazard assessment data into a risk assessment must then similarly be documented.

Since the scope of TSCA exerts severe pressure on the operation of OTE, the role of research in testing and evaluation becomes complex. Approaches which have proven successful in the limited case for pesticides and certain other known toxicants must now be extrapolated to a multitude of chemicals (the estimated number of which is 7×10^4). The difficulty inherent in this extrapolation is that for known toxicants, toxic hazard is well-defined and environmental dispersal may be anticipated, whereas for the greater multitude of chemicals, toxic hazard is still undefined and environmental dispersal may or may not occur. Although this difficulty is present, past experience suggests that environmental protection (e.g. risk assessment) may be achieved by judiciously examining the ambient concentration in the environment through a careful exposure assessment, and comparing the effects of the chemical (through a dose-response relationship) to the environmental concentration. Selection of the appropriate effects to be evaluated and the criteria by which these might be employed form the basis of hazard assessment. The actual synthesis of exposure and hazard assessment is called the risk assessment process.

As hazard and exposure assessment are not completely separated, both are also linked with health hazard assessment in many phases. On a practical level, however, research to provide the data and relationships must be segregated into parcels and packages of closely associated subject matter and methodology. Exposure assessment consists of determining or estimating the environmental loading, the physical/chemical properties of the chemicals, the nature of the chemical and biological transformations, the nature of the transport processes, and the nature of the significant environmental characteristics impinging on these processes. These data and processes must then be integrated into validated models which provide the estimates of environmental concentration in time and space. Environmental concentration estimates must have the form of projected surfaces which will enable the operational office staff to examine the implications of environmental partitioning and transport processes over time and under various environmental conditions. The estimation models must be user-acceptable and user-accessible and be supplied with adequate documentation. Moreover, the validity of the models in regard to actual field situations depends on the understanding and agreement of all parties concerning the implications of the data and the criteria applied to the utilization of the models.

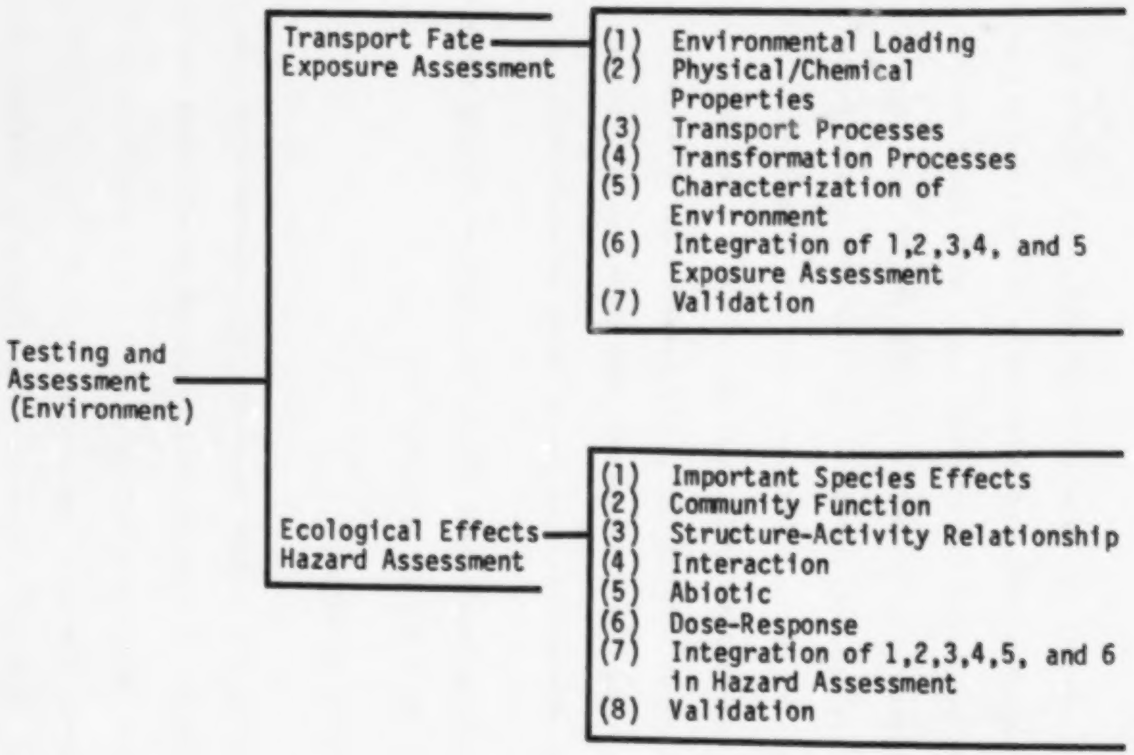
Hazard assessment must take into account important species effects, since these are known to be the principal drivers of the legislation and its effective implementation. Hazard assessment must be cognizant of the effects on community function, abiotic effects (e.g. stratospheric modification), the interactions between chemicals regarding various effects, and finally the dose-response relationships which can be applied in the overall hazard assessment. The dose-response relationship, supported and documented by knowledge obtained in the field concerning the significance of these effects, is then coupled with the estimated environmental concentrations (the aforementioned surfaces) to provide the risk assessment. The risk assessment can take into account safety margins, multiple pathways of exposure, and other significant variables in establishing risk.

The operational assessment approaches of OTE and the research and development approaches of OEPER serve as complimentary functions. OEPER provides the test methodologies, the evaluation criteria, and the interpretative relationships for OTE; OTE in turn helps guide the priorities and most practical approach within that research and development program to achieve their operational ends. OTE's approach can be adjusted and updated as new research provides the tools and technologies; adjustments in the research and development program can be made to adequately accommodate some shifts in priorities to meet the demands of administrative law or other interpretations of TSCA.

Informational needs and future research for the environmental program are outlined in Figure 5-1.

A. RESEARCH PRIORITIES

During the initial phase of TSCA implementation, the greatest emphasis of the research will be placed on providing technical assistance to OTE in developing testing protocols and models for determining the ecological effects of toxic chemicals. As the implementation program matures, emphasis will shift to validation of testing models and protocols, refinement of the methodologies, and maintenance of cost-effectiveness and simplicity. In general, the test protocols will be incorporated into test rule development and testing guidelines.



RESEARCH STRATEGY INFORMATIONAL NEEDS

Testing and Assessment (Environment)
Transport Fate Exposure Assessment
(1) Environmental Loading
(2) Physical/Chemical Properties
(3) Transport Processes
(4) Transformation Processes
(5) Characterization of Environment
(6) Integration of 1,2,3,4, and 5 Exposure Assessment
(7) Validation
Ecological Effects Hazard Assessment
(1) Important Species Effects
(2) Community Function
(3) Structure-Activity Relationship
(4) Interaction
(5) Abiotic
(6) Dose-Response
(7) Integration of 1,2,3,4,5, and 6 in Hazard Assessment
(8) Validation

FIGURE 5-1. RESEARCH STRATEGY ENVIRONMENTAL INFORMATIONAL NEEDS AND FUTURE RESEARCH

The research program will also take into consideration the needs of the Office of Enforcement and particular problems experienced by the EPA Regional Offices. Thus the program must develop a capability for handling special problems and emergency situations related to toxic chemicals in Regions throughout the United States.

B. PROGRAM STRUCTURE

Environmental research on toxic substances is being carried out under two categories: Toxics - Transport and Fate; and Toxics - Ecological Effects. The goal of transport and fate research is to provide cost-effective and improved methodologies for predicting transport, transformation, movement, and persistence of toxic chemicals in the environment. Transport and fate methodologies will be used to develop testing protocols and exposure assessment models for defining environmental concentration of toxic chemicals. The Toxics - Ecological Effects research goal is to develop cost-effective and improved methodologies for measuring the effects of toxic chemicals on the environment. Ecological effects research will lead to the development of testing protocols and hazard assessment models for defining toxic hazard. In early FY 80, research on the development of measurement techniques for defining human exposure to toxic chemicals in the ambient environment was initiated under the Public Health Initiative.

Transport and fate and ecological effects research in ORD is administered by OEPER and is being carried out in its seven laboratories. These seven laboratories provide capability for research in various media:

- Freshwater - Athens, GA; Corvallis, OR; and Duluth, MN
- Marine - Gulf Breeze, FL; Narragansett, RI; and Corvallis, OR
- Terrestrial - Corvallis, OR; and Ada, OK
- Ground Water - Ada. OK
- Air - Research Triangle Park, NC

In addition, the work on methodologies for human exposure to ambient toxics is being conducted by the Environmental Monitoring and Systems Laboratories in Las Vegas, NV; Cincinnati, OH; and Research Triangle Park, NC; and the Health Effects Research Laboratories at Research Triangle Park, NC, and Cincinnati, OH.

II. TESTING AND ASSESSMENT

The Toxic Substances Control Act contains several features which implicitly require the acquisition of chemical fate information. Such information is useful in conducting fate assessments for both existing and new chemicals. One of the key determinations, in either case, will be the exposure assessment or estimated environmental concentration (EEC).

One of the many elements which determines EEC is the fate of the chemical in the environment(s) under consideration. Fate, in turn, may be viewed as consisting of transport and transformation characteristics. An analysis of potential transport mechanisms leads to the conclusion that certain physical and chemical data should be considered.

Recent research on aquatic transport and transformation processes for trace chemicals; the development of hypotheses, concepts, and strategies for conducting exposure assessments; and the development of new and improved analytical methods have greatly advanced the state-of-the-art for exposure assessment. Unfortunately, the level of knowledge is not uniformly distributed across the various environments. In addition, the concepts and procedures developed for determining or predicting the fate of toxic chemicals have not been in use long enough to gain general acceptance by the scientific community or the various regulatory authorities.

Thus, the objectives of the testing and assessment portion of the research strategy for environmental exposure are as follows:

- Describe the scientific concepts, technology, and information required in environmental exposure analyses for toxic chemicals.
- Identify the current state-of-the-art and information gaps in exposure analysis.
- Outline the research and development strategy for extending, improving, and simplifying the concepts, methods, and information bases required.

Releases of hazardous chemical substances into the environment during manufacturing processes, distribution, use, or disposal (whether accidental or planned) can have adverse impacts on both natural and man-modified ecosystems and their components. The social costs may include degradation of the environment; losses in sport, commercial fishery, and wildlife resources; decreases in agricultural production, losses in tourism and devaluation of property values, and other adverse impacts.

The potential ecological effects of chemical substances are exerted differently upon diverse life forms, as well as at various levels of biological organization including subcellular, cellular, organismal, population, community, and ecosystem levels. Testing for such effects requires the selection of indicators (i.e. indicative parameters) that provide for wide taxonomic representation and include a range of biological processes, or that have validated application (productive capability) to these parameters.

Levels of ecological organization above the individual species can provide information directly related to ecological consequences of the release of a hazardous chemical. However, the development and standardization of tests for such effects is difficult due to the complexity of the species interactions that characterize ecosystems. A major thrust for the research program for ecological effects, therefore, will be the development of test methods that address interactions such as those which occur between predator and prey, among competitors for habitat or food, and between disease and host organisms. As methods such as microcosm studies and other laboratory model systems are developed and validated they will help to address these ecological testing needs.

Laboratory testing below the level of the organism is also potentially useful, generally rapid, and readily amenable to standardization. The majority of such testing, however, needs further development to be usable for ecological impact assessment. Since many cellular and subcellular functions are common to a wide range of organisms, they have the potential of being applicable to many sets of ecological circumstances. Therefore, the development and validation of a number of cellular and subcellular tests are being considered for inclusion in the research program.

Most ecological effects tests currently in use employ single species test populations of vertebrates, invertebrates, or plants. Individual species represent an intermediate level of biological organization between cellular and subcellular functions and community/ecosystem interactions. Many single species tests are considered to be state-of-the-art methods and have correlated well with actual ecological effects of chemicals. As a consequence, the continued development and validation of single species tests will be important components of the research program for ecological effects.

An important emphasis of the hazard assessment research program, working in concert with the research program for chemical fate, will be upon the determination of which system(s) of hazard evaluation, exposure evaluation, and risk assessment provide the necessary and sufficient information for recommending possible regulation. This includes the identification of the best available criteria to be applied in utilizing these approaches, and how scientifically-defensible risk assessments may be accomplished in the most cost-effective manner.

All aspects of testing and assessment development to be supported by the hazard assessment research program must include in the research design a demonstration(s) of linkage with effects of toxic substances upon elements of the real environment, thus establishing a measure of the predictive capability of the research product. This approach will produce legally-defensible tools with which the mandates of TSCA may be implemented.

A. TRANSPORT AND FATE (EXPOSURE ASSESSMENT)

1. Background and Status

The determination of environmental exposures is an integral step in any risk analysis or toxic substance regulatory/control decision which attempts to tie the volumes and distribution of materials entering the environment to specific adverse human health or environmental effects. As a corollary, reliable exposure analyses require valid estimates of the loading rates of toxic materials into the various environmental media.

Once in the environment, the distribution, concentrations, and persistence of a toxic substance at any point in time are the net result of physical, chemical, and biological processes that transport and transform the pollutant either simultaneously or in sequence. The rates at which these processes actually affect a material are functions of its physical/chemical properties and the biotic and abiotic conditions present in the receiving environments. Although a number of processes can theoretically affect a chemical's fate, only a few may be significant for any particular chemical and/or environment. It is important to note that both the identity and magnitude of the predominant "fate" processes affecting a chemical can change drastically from one environmental system to another.

For many existing chemicals whose loading patterns have been established, properly designed monitoring programs can provide environmental concentrations and exposure estimates. In order to extrapolate from monitoring data, minimal knowledge of (1) the dominant fate processes involved, (2) the physical/chemical properties of the materials, and (3) the characteristics of the receiving environment must be available. For new chemicals, estimates of environmental loadings must be based on projected production, use, and disposal patterns.

The most important aspect in predicting environmental exposure is the development and application of valid strategies, techniques, or models to assemble, integrate, and assess the various complex data sets required.

Thus, the research activities required to provide the scientific basis for making valid quantitative estimates of human and ecological exposure to toxic substances entering various environmental media include:

- Development of improved concepts and techniques to determine or estimate environmental loadings.
- Development of improved concepts and methods to characterize the dominant transport processes.
- Development of improved concepts and methods to characterize the dominant transformation processes.
- Development of improved laboratory methods to determine the physical/chemical properties of toxic substances.

- Development of concepts and methods for optimum characterization of environments.

- Integration of the above in developing exposure assessment models.

- Development of concepts, methods, and information requirements for testing and validating exposure assessment models, laboratory methods, and field observations.

- There is a need to make available analytical techniques to be used in carrying out fate, effects, and exposure assessment studies for many toxic chemicals in their fresh-water, estuarine, terrestrial, and biota environments. For many toxic chemicals, measurement techniques for identification and quantification are not available.

2. Research Strategy

a. Environmental Loading (Emissions) Estimates

Chemicals may enter the environment: (1) at the time of production through direct losses from the production process (i.e. discarded solid, liquid, or gaseous waste products); (2) when the principal manufactured material is packaged, transported, and/or delivered to intermediate or final users (accidental spills, etc.); or (3) when the product or products containing the materials of concern are used and discarded.

For some materials, precise information may be available on the rates of discharge into various compartments of the environment. For most materials, however, estimates must be made which consider the projected volumes produced or imported and the anticipated distribution, use, and disposal patterns. Regardless of the type of data, the procedures or models used for loading analysis should integrate and reduce the pollutant inputs to time-series concentrations at specific locations for the aquatic, atmospheric, or terrestrial media. The accuracy of the time functions is extremely important and is dependent on both the fate and the effects of the chemical in the environment.

b. Transport Processes Characterization

To obtain valid exposure estimates, an understanding of and characterization of the significant transport processes which impact chemical distribution and exposure in any environment are essential. Characterization in this sense requires that (1) the process be identified, (2) cost-effective laboratory procedures be developed to determine the rate and extent of the process within anticipated ranges of environmental conditions, (3) protocols be written describing the laboratory characterization procedures; and (4) interlaboratory testing and evaluation of the protocols be conducted prior to final acceptance and general application.

As the dominant transport processes in general environments are characterized and protocols completed, other processes which may dominate selected exceptional environments will be investigated.

Processes which may be important in the environmental transport of a chemical include volatilization, partitioning adsorption/desorption with soils and sediments, solutions/disolution, advection, dispersion, precipitation, sedimentation, deposition, and scour.

Suitable methods for the determination of octanol/water partition coefficients, soil thin layer chromatography (TLC), and soil adsorption isotherms are currently under development. Methodologies also need to be developed for measuring volatilization rates, leaching potential, and the uptake of chemicals by biota.

Identification of those circumstances in which expensive laboratory testing can be avoided through the use of structure/activity relationships (SAR) or estimation techniques by which existing chemical and physical data can be used to calculate some other parameter is highly desirable.

Most of the test methods which appear suitable for the development of transport data are not standardized. Thus, evaluations and validations of these procedures through mechanisms such as interlaboratory testing ("Round-Robins") are needed.

The effects of salinity and other constituents present in marine water on transport processes is poorly understood. Transport and fate protocols need to be tested for freshwater vs. marine systems.

The atmospheric fate of hazardous and toxic chemicals is determined by competing physical and chemical processes. Physical processes responsible for the transport and removal of chemical compounds include dilution, dry deposition, adsorption to particulates, and rainouts. A rapid reduction in the concentration of gaseous emissions is a result of dilution; however, dilution does not cause any loss from the atmosphere in the chemical's mass. Dilution affects all chemical compounds equally, whereas other physical processes are compound-specific. Dry deposition is important for those chemical compounds which react with or are adsorbed on surfaces such as soils, plants, bodies of water, and man-made structures. The fate of the chemical compound adsorbed on a particulate is determined mostly by the fate of the particulate, which is subject to rainout, conglomeration, and fallout. Desorption of the chemical compound from the particulate is also possible, because dilution reduces the concentration of free compound around the particulate. Rainout affects chemical compounds which are highly soluble, thus resulting in contaminants deposited in water bodies or on land.

c. Transformation Process Characterizations

Exposure analysis procedures must also include quantitative descriptions of the significant physical, chemical, and biological transformation processes. The significant processes must be identified; cost-effective laboratory procedures must be developed to obtain the rates and extent of the processes within anticipated ranges of environmental conditions; protocols must be developed describing the laboratory characterization procedures; and interlaboratory testing and evaluation of the protocols must be conducted prior to final acceptance and general application. These transformation process protocols may be very complicated since several different analytical procedures may be required to quantify the same reaction kinetics. How many different procedures are needed depends on the physical/chemical properties of the toxic substance and the environmental media of interest. Thus, successful application of these protocols may depend on the analyst's ability to select an appropriate set of standard laboratory procedures.

The significant mechanisms for the environmental transformation of synthetic chemicals are hydrolysis, photolysis, biodegradation, and abiotic oxidation/reduction reactions.

Suitable methods exist for the evaluation of hydrolysis and aqueous photolysis. However, appropriate methodologies or improved procedures need to be established for atmospheric photolysis, biodegradation, and atmospheric oxidations. A need is also apparent for research on the significance of abiotic reduction and free-radical oxidation in water and soils. With respect to biodegradation reactions, there is a need to determine the importance of anaerobic biodegradation in the environment, and to develop and refine laboratory methods which can be used to predict environmentally relevant biodegradation rates.

Studies should be conducted to ascertain the extent to which structure/activity relationships can be used to predict hydrolysis, photolysis, and free-radical oxidation reactions.

The test methods currently available for the development of transformation data and those which will be developed are not yet standardized and will need to be evaluated and validated. Hydrolysis and photolysis tests are at such developmental stages where Round-Robin testing may be initiated. The overall importance of anaerobic biodegradations in the environment needs to be determined, and the ability to determine biodegradation rates or rate constants in the laboratory which can be related to real world conditions needs to be improved. Studies need to be conducted on the importance of acclimation and the role of concentration vs. biodegradation. Another important research need is for a "toxicity screen" procedure. This procedure will permit the introduction of some appropriate species into a test chamber where biodegradation (or some other transformation process) has occurred, and will "screen" for the loss, continuation, or enhancement of original toxicity. Round-Robin studies are needed for most state-of-the-art methodologies.

New methods on aquatic and atmospheric systems need to be developed and current methods improved to define better the significance of reactions on water and soils, and to develop structure/activity relationships between chemicals and their susceptibility to free-radical reactions.

Since the effects of salinity and other marine water constituents are not well-defined, a comparative evaluation of the rate constants for hydrolysis, photolysis, biodegradation complexation, and oxidation/reduction in freshwater vs. marine systems should be carried out.

Chemical transformation processes important in the troposphere include reaction of compounds with OH radicals, with ozone, (O_3) and to a much lesser extent with species such as RO_2, HO_2, atomic oxygen, singlet molecular oxygen and oxides of nitrogen (NO_x). Data needed to assess the lifetimes of toxic compounds in the troposhere are now obtained from estimates or measurements of OH radical and ozonolysis reaction rates. The need exists for better estimates and for a means of actually measuring the OH radical and ozonolysis reaction rates for various toxic compounds. Also to be identified are reaction products.

Those chemical compounds which are reactive, that is, have half-lives of a day or less, can occur at elevated concentrations only within the boundary layer of the atmosphere. For these compounds, it would be necessary to investigate the possibility that degradation products of a toxic nature might form at levels problematic to human health.

Certain chemicals absorb sunlight directly and undergo photolysis reactions. To assess tropospheric photolysis, solar radiation intensity and spectral character must be estimated or measured along with the adsorption efficiencies of compounds at various wavelengths. The gas phase photolysis rate and reaction products need to be established to estimate atmospheric photolysis lifetimes in the troposphere. Additional research is needed to establish photolysis rates of compounds on adsorbed materials and to determine if any synergistics such as the photolysis of copollutants can induce the decomposition or transformation of original toxic compounds.

In the stratosphere, important processes involve reaction of toxic compounds with atomic oxygen $O(^1D)$, and photolysis in the 150 nm to 300 nm region of the solar spectrum. Significant in stratospheric photolysis are solar radiation intensity and spectral character, and the adsorption efficiencies of absorbing compounds at various wavelengths.

d. Physical/Chemical Properties of Toxic Chemicals

Simple physical/chemical properties of toxic compounds are important and may provide good information on the potential fate of chemicals in the environment. Physical/chemical properties provide an initial indication of which of the various transport, transformation, and human and environmental test protocols should be utilized. Such shortcut procedures may be useful in the cost-effective testing of large numbers of chemicals; however, each decision procedure must be thoroughly evaluated and tested to assure that significant exposure and/or effects are not overlooked.

Standard laboratory methods for measuring many of these physical/chemical properties are well accepted by the scientific and industrial community; yet, the selection of appropriate analytical methods may depend upon the magnitude of the constants and the precision and accuracy of the methods. Important properties include water solubility, vapor pressure, boiling point, melting point, particle size, molecular dimension, molecular diffusivity, and partition coefficient. For the purpose of defining environmental transport of chemicals, the data on water solubility, vapor pressure, and partition coefficients are especially important. Although satisfactory methods exist for most of the physical/chemical properties measurement, Round-Robin validation of such methods is needed.

e. Environmental Characterizations

Both the rates and extent of transport and transformation processes are impacted by the physical, chemical, and biological characteristics of the receiving environments (e.g. air, water, soil, temperature, pH, biomass, volume, area, depth, etc.). Thus, new and improved concepts and methods must be developed to identify, measure, and catalogue these parameters in the simplest detail required to describe quantitatively the environments of interests. Since many of these parameters fluctuate at least seasonally, maximum, minimum, and time-averaged values become important.

Previous ecosystem studies and environmental monitoring programs provide the basis for characterizing site specific environments (e.g. a particular air shed, river beach, lake, estuary, etc.). However, new methods must be developed, evaluated, and tested to reduce the characteristics of a large number of environments into a minimum set of simple hypothetical (canonical) descriptions for calibrating exposure assessment models.

f. Exposure Assessment Models

The state-of-the-art of exposure assessment models is not well-developed. Attempts are underway to integrate loading information with data on transport and transformation of chemicals to produce suitable models. An Exposure Analysis Modeling System (EXAMS) developed by the Agency predicts concentrations of toxic chemicals in water. EXAMS is being tested for various chemicals and is also being refined to improve its resolution. Corresponding models need to be created for air and terrestrial environments. To date, most air models are based on simple dispersion and transport characteristics. These models should be replaced by site specific and generic models. Finally, models describing concentrations of toxic chemicals in multimedia environments must be developed.

Screening procedures based on structure/activity relationships, representative groups, and pattern recognition methods are needed to provide rapid estimation of exposure and fate of chemicals in the environment. These models will be particularly helpful in evaluating new chemicals under Section (5) of TSCA.

Models describing pathways and concentrations of toxic chemicals are also needed to assess the total exposure of toxic chemicals to the environment. Finally, the exposure assessment models must be coupled with ecological effects data in order to develop risk models.

g. Validation

A model is a logical and/or mathematical simplification of a real-world system. Models may be either predictive or descriptive in nature and can be used for designing environmental monitoring systems and clean-up procedures for pollutant spills, or for evaluating potential hazards of new chemicals. In the first stage of validation, it must be verified that the logic and/or mathematics of the model do not contradict any principle of the subject field. In the second stage of model validation, field collected data are used to exercise the model. Model derived output values are then compared to actual measurements of ambient conditions. The following factors should be considered in the third stage of model validation:

- Determine those areas for which modeling can provide a more cost-effective means of acquiring needed information.
- Determine the criteria for evaluation of the model, i.e. the level of confidence that will be acceptable for the intended use.

- Review and evaluate existing models and identify further developmental requirements.
- Obtain good reaction rate constants which are measured and verified. It is essential also to have good reaction product characterization. Local area model validation can use wind-tunnel/water-channel simulations. Microcosms and laboratory ecosystems are needed for testing of models. Microcosm testing may provide first indication of the validity of the model.

Field validation of models is also necessary before a model can be used by the Agency in the regulatory decision-making process. When field-study data are used to validate models, quality assurance must be emphasized to obtain good quality data. If methods change with time, full-fledged comparisons and validations of old and new methods must be undertaken. Field studies should be undertaken to provide background concentrations for all models (local, regional, and global).

3. Research Program

Research in the area of exposure is designed to meet the immediate needs arising from TSCA implementation as well as from the development of methodologies for controlling long-term environmental pollution problems. Some of the important needs identified by OEPER as resulting from TSCA requirements are: (1) technical assistance to OTE so that the implementation of TSCA can be carried out on a sound, credible, and scientifically-defensible basis; (2) testing methodologies for predicting the fate of chemicals in the environment (such tests must be cost-effective, simple to perform, and based on scientifically-sound principles); and (3) models for estimating or predicting exposure concentrations of toxic chemicals in the environment (such exposure data are essential in defining the risk toxic chemicals may pose to humans and the environment).

One portion of the ORD resources allocated for exposure assessment is designated for the provision of direct technical support to OPTS. Technical support is a critical service because OPTS in its initial stages of operation must develop guidelines, evaluation schemes, and other testing and assessment documents. Since the area of exposure assessment is still in a developmental stage, it is essential that ORD work closely with OPTS to develop guidelines and testing schemes that are scientifically-defensible. Technical assistance may include aid in the development of the scientfic logic for testing and assessment, technical support in document preparation and/or review, workgroup participation, chemical evaluation support, special testing, site visits, serving as expert witnesses, and computer model document and user support.

Testing methodologies for predicting the fate of chemicals in the environment are necessary to provide data for exposure assessment. Fate tests provide critical information on what happens to a chemical once it is introduced into the environment, in which part of the environment (air, water, soil, and/or biota) the chemical may accumulate, and for how long and in what form the chemical may persist. Chemical fate testing methodologies are currently being developed for incorporation into testing schemes under Sections 4 and 5 of TSCA. In developing such methodologies, emphasis is placed on scientific soundness, cost-effectiveness, rapidness, and relative ease of performance.

The most important areas for which testing methodologies are needed include: atmospheric reactions; the transport, transformation, and movement of chemicals in soils/sediments; biodegradation of chemicals; photolysis; range-finding screening methods; transport and transformation via the food chain system; and structure/activity concepts for fate prediction. Work on the atmospheric fate of chemicals involves the development of predictive techniques and laboratory test methods, as well as environmental sampling techniques. Effort in the area of transport, transformation, and movement of chemicals is concerned with the development of improved methodologies for predicting adsorption/desorption and leaching of chemicals in soils/sediments. Biodegradation studies are designed to define the half-lives and transformation of toxic chemicals in terrestrial, fresh-water, estuarine, and marine environments.

ORD has initiated several projects to define the fate of toxics in the food chain. The information obtained will be used to develop food chain models and testing methods. ORD has also initiated a program to develop structure/activity concepts for predicting the fate of chemicals based on physical/chemical properties and structural characteristics.

Mathematical models also need to be developed and improved which can be used to integrate and validate the testing methodologies. Mathematical models for estimating the environmental loadings, exposure, and effects of chemicals are being developed, improved, and evaluated by ORD. These models represent quantitative hypotheses of chemical entrance into various environmental media, their transport, degradation and distribution, and human and environmental impacts.

Exposure assessment models are being developed to predict the concentrations of chemicals in air, surface waters, sub-surface waters, marine environments, soils, and sediments. A program which closely parallels OPTS needs is being initiated under the Public Health Initiative to develop models for defining the movement and concentration of chemicals in the food web and to develop methodologies for measuring human exposure to toxic chemicals present in the ambient environment. Specific investigations under the Public Health Initiative include the development of an air model, water model, terrestrial model, multi-media models, food chain models, transport and transformation models, exposure assessment methodology, and microcosms for the validation of models.

Basic Research Goals

- Development of laboratory methods for determining atmospheric reaction rates of organic chemicals with free radicals. (Highest Priority)

- Work to determine the effects of halocarbons on ozone levels in the troposphere/stratosphere. The dispersal and removal of man-made halocarbons will be described by a mathematical model that combines the atmospheric chemical transformation with physical transport mechanisms. This model will be able to predict the impact of substitutes for freons on stratospheric ozone and will be able to aid in designing various control options. The photodissociation rates and mechanisms of halogenated compounds under stratospheric conditions will be examined. (Highest Priority)

- Determine of the distribution of halogenated compounds in the troposphere by sampling of selected urban, rural, and maritime areas. Another project will focus on developing degradation models from an analysis of photolysis rates and reaction products under laboratory conditions. (High Priority)

- Evaluate sorption properties of soil/sediments as they relate to the correlation of adsorption with organic content, cation exchange capacity, solubility, and the n-octanol-water partition coefficient. (Highest Priority)

- Develop protocols for leaching of chemicals in soils. These protocols will provide a methodology for testing chemicals for leaching in soils and for their potential as groundwater contaminants. Procedural modifications required to adapt these protocols for use with toxics will be identified and documented in detail. Procedural and operator variability will be identified and procedures developed to reduce their impact. (Highest Priority)

- Investigate the adsorption of charged and protonated organics in natural sediments. Emphasis is on relating the sorbent properties with cation exchange capacity, particle size, organic carbon, ionic strength, and pH. Sorbate properties include solubility, molecular structure, and size. (High Priority)

- Conduct studies on the biodegradation properties of estuarine microorganisms and their impact on the fate of toxic chemicals. (Highest Priority)

- Determine the rate of degradation of chemicals under conditions of anaerobiosis with emphasis on defining microbial kinetics for degradation. (Highest Priority)

- Evaluate the importance of co-metabolism in the microbial degradation of chemicals under varying environmental conditions. (High Priority)

- Define the role of sensitizers as well as the effect of sediments on solar radiation in water. (Highest Priority)

- Develop, evaluate, and validate, for differing environmental simulations, range-finding systems (e.g. Eco-core) for determining the transport and transformation of organic chemicals in laboratory-maintained environmental samples which integrate all fate processes into one aquatic system. (Highest Priority)

- Bioaccumulation models must be developed which employ basic physico-chemical and biochemical measurements to predict bioaccumulations and potential residues. (Highest Priority)

- Transformation processes in plants and animals, particularly conjugation and covalent reaction can result in retained residues or bioactive products. Investigation of the major components of food chains will be based on studies in both large and small scale microcosms and modular food chain systems. After early studies on simple (primary producer/herbivore; herbivore/carnivore) systems, studies on more complex systems involving birds and fish will be attempted for multi-media assessment. (Higher Priority)

- Predict degradation based on the structure of toxic chemicals. Coordinate studies of structure/activity relationships between various microsomal (plants, insects, mammals) and chemical (free radical, UV, peroxide) oxidation systems. Predict plant uptake and transport and transformation based on structure/activity relationships. (Highest Priority)

- Water Model: Some progress has been made in the development of water models.

  -- The Exposure Analysis Modeling System (EXAMS) has been developed to predict the concentration of chemicals in freshwater systems. (Highest Priority)

  -- Continue development of models to predict movement of toxic chemicals in the Great Lakes. (Highest Priority)

- Estuarine Models: Continue efforts to develop mathematical sub-models generated from other projects which can be appropriately inserted into existing estuarine hydrodynamic models. (Highest Priority)

- Continue development of models to predict transport amd transformation of chemicals in estuarine and marine environments. Initial emphasis will be placed on defining the rate parameters followed by development and validation of the models. (Highest Priority)

- Air Model: Continue development of a numerical model for predicting concentration of toxic chemicals in air. The model is based on transformation of chemicals coupled with transport and diffusion data. (Highest Priority)

- Terrestrial Model: Continue work to develop T-EXAMS (analogous to EXAMS for water) for predicting concentrations of chemicals in terrestrial environments. (Highest Priority)

- Develop mathematical models for transport and transformation of chemicals in saturated and unsaturated soils. Mathematical models will be developed to describe selected mechanisms for chemical attenuation for both steady state and transient hydraulic conditions for one-and-two dimensional flow geometries. (High Priority)

- Multimedia Models: Continue attempts to develop a first generation model for defining exposure concentrations of toxic chemicals in multi-media environments. The development of a comprehensive integrated multi-media model will require a long-term research approach with considerable resources. (Highest Priority)

- Food Chain Models: Continue work on defining pathways and concentrations of toxics in food chain systems. This work involves the measurement of uptake of chemicals in plants, studies of bioaccumulation of chemicals in fish, marine animals, avian species, etc., and finally, integration of this information with transformation parameters to develop a model. (Higher Priority)

- Exposure Assessment Methodology: Continue work under the funding of the Public Health Initiative on developing methodologies to measure human and environmental exposure to toxic chemicals present in the environment. This work involves the measurement of ambient concentrations of toxic chemicals in air, water, soil, and the food chain. (Higher Priority)

- Microcosms for Validation of Models: Continue development of laboratory microcosms (aquatic, terrestrial, and estuarine) for the validation of mathematical models. Specific work includes:

-- The use of large and small microcosms in the validation of models to be complemented by field studies on a limited number of chemicals. These systems will be tested using existing field data, where possible.

-- Microcosms will be designed to simulate terrestrial, surface freshwater, ground water, estuarine, and wetland environments.

-- Field studies may include the continued use of existing field channels. (Highest Priority)

Future Research Goals

- Interlaboratory validation of methodologies for measuring physical/chemical properties of toxic chemicals.
- Interlaboratory validation of tests for defining transport and transformation of chemicals in the environment.
- Validation of exposure assessment models using laboratory model ecosystems, mocrocosms, and field studies.
- Increase emphasis on structure/activity relationships and other estimation techniques for predicting the fate of chemicals.
- Refinement of the methodologies for predicting transport and transformation of chemicals.
- Development of a long-range research program to meet the future needs of TSCA.

B. ENVIRONMENTAL EFFECTS (HAZARD ASSESSMENT)

1. Background and Status

As recognized in numerous sections of several Congressional acts (including TSCA) EPA is charged with the responsibility to protect public resources as well as biological integrity, e.g. "balanced indigenous populations" and the like. To protect specific components of natural systems, a different data set is required than for cases where an "ecosystem" is to be preserved. For example, the data needed to control air emissions to protect agricultural crops are more specific and restricted than the data needed to protect northern coniferous forests or grasslands. Similarly, information needed to protect trout populations for sport fishing is more specific than information needed to protect the balanced indigenous populations of a water body.

Past regulatory efforts have relied heavily on data sets for one or a few species, assuming that if these species are protected the necessary supporting organisms will be able to thrive under similar conditions. However, unless adequate data are developed to assure protection of those specific processes required to protect the selected species, their protection will not be assured even though the community is healthy. The concern here is with population protection as distinguished from community protection.

To achieve our goal requires us to identify the species important to man as objects of regulatory decision-making before we can decide the necessary data sets. This task is simple for domestic organisms such as White Pine, corn, salmon, and sheep. Likewise protection of endangered species such as the golden eagle and snail darter is mandated by law. Many decisions are much more difficult, e.g. how does one decide if Pocket Gophers or Wild Roses are among the important species? Once a list of important species is estabblished, "indicator" species and surrogates must be identified since resources are not available to test them all.

Communities are viewed by many in a manner analogous to the view of an organism, i.e. they have functions such as primary production, respiration, decomposition, and aging just as organisms have metabolism, breathing, and growth. Community functions are dependent on many species and species interactions which are complexly intertwined, so that a change in one place may have a ripple effect throughout the whole community. For communities, individual species are less important than the community functions, regardless of which subset of species may accomplish that function. For example, instead of the mortality rate, growth rate and number of eggs produced, biomass, R/P ratios , and predation rates may be used to measure community response. Protection of biological integrity and similar goals can only be achieved by community protection, but these goals do not ensure that an aesthetically desirable species to man will thrive.

The number of communities is probably as large as the number of different species, so the first problem (as for single species) is to decide which species can be used as indicator or "type" communities and which can be used as surrogates since all cannot be tested. However single species and microcosm tests cannot be equated with protection of important species and communities. The protection of species and communities are objectives, whereas single species and microcosm tests are techniques.

In addition, judgment of the effects of a chemical placed in the environment cannot be made as though the chemical were the only stress to be considered. In nearly every locale, other man-made contaminants as well as natural stress will exist. The impact of these other stresses on the effect of concern must be included in the final evaluation.

Some effects may occur that are abiotic (e.g. damage to structures from acid rain) or that have indirect biological effects such as ozone depletion and subsequent radiation effects. These effects also need to be identified and included in the decision-making process.

As practical decision-making proceeds, experience likely will show that there will not be a single environmental concentration, but many. The expected ambient concentrations will vary over time. Therefore, effect concentrations expressed as single numbers may be an inadequate basis on which to judge the safety of expected ambient concentrations. Rather, a family of curves or response surfaces will be required to integrate time of exposure into acute, sub-chronic, and chronic toxicity as well as behavioral changes, bioaccumulation, and seasonal considerations.

The generation of such response surfaces requires different data which are more difficult to obtain than data needed for threshold values for use under worst case conditions. The state-of-the-art to generate such information is poorly developed.

The above generic informational needs appear to be the more important ones that must be fulfilled for decision-making under TSCA.

For new chemicals, reliance will have to be placed on laboratory tests and predictive techniques such as models, whereas for existing chemicals, experience and monitoring data can substantially increase the basis for decision-making.

2. Research Strategy

a. Important Species Effects

A number of reliable single species tests have been developed for important organisms such as sport and commercial fishes and a select few of their food organisms. Similar tests are available for measuring stimulatory or inhibitory effects for aquatic algae and a few terrestrial plants. Some species such as the salmonid fishes are obviously important and have been shown to be quite sensitive to toxicants. With the invertebrates, it is not so evident that we have the most sensitive species in the test protocols. In fact, some would suggest that the species which have been tested are most amenable to being raised in captivity. Present research concentrates on three areas: (1) Round-Robin testing of those tests which are well developed to ascertain whether the methods are adequate and to give an idea of the variability which might be expected among laboratories; (2) development of new tests for species which represent special niches such as sediment-dwelling aquatic organisms; and (3) development and validation of shortcut methods to reduce the time and cost of testing. Important factors influencing the definition of informational needs in this area are (1) the number and kinds of species, (2) significance of end points, (3) estimating species sensitivity, and (4) residues, tainting, etc.

(1) Number and Kinds of Species

Resource constraints will allow testing of only a few important species. A principal need is to identify which species should be tested, based upon the utility of the data that would be obtained, and to verify that these choices adequately represent the species to be protected.

To date, except for cultivated species, those species most used for testing have been chosen based upon laboratory adaptability, curiosity, or availability. The number of important species among plants and animals is highly variable within and between terrestrial, freshwater, and marine habitats.

Suitable test conditions are most easily developed for species that have been cultured, domesticated, or managed in some manner. For others, such as marine invertebrates, the problems are more numerous.

(2) Significance of Endpoints

A myriad of endpoints have been proposed or used to assess effects in toxicity tests. Increased mortality or reduced growth have been more useful for regulation purposes than more subtle changes in physiology or behavior. Any change from normal, however, may be detrimental. This is more apparent for communities than for single species. In fact, many practices in domestic animal production, such as using growth hormones, depend on a change from normal to improve utility.

Whatever the effect measured in a toxicity test, the ultimate concern is the impact on the population and its quality (size, taste, vigor, etc.), and the effects of this input at the ecosystem level. To date, little concern has been given to the population significance of small mortality differences or reproductive impairment, to say nothing of physiological changes or alterations in behavior.

Establishing the significance of commonly used or potentially convenient endpoints to populations is a high priority. In this area, dose-response significance is needed rather than "all or none" judgments if the expected effects are to be related to ambient concentration predictions. Such evaluations will require use of large experimental systems in which whole populations can be tested. For bacteria, the size of the system needed is not large; however, for larger plants and animals, systems of acres or square miles in size may be necessary. Data for these evaluations may be obtained more efficiently from chemicals already in use rather than in experimental systems. A good example of this approach is the demonstration of the significance of egg shell thinning caused by DDE.

A high priority is to focus effort towards the goal of validating the populational significance of currently used endpoints.

(3) Estimating Species Sensitivity

As a result of examining the large data base for the toxicity of consent decree chemicals to aquatic life, the range of sensitivity to a given chemical among aquatic life species was frequently observed to be much larger than the difference observed between acute and chronic toxicity. If the total range of species sensitivity due to terrestrial organisms and bacteria could be included the difference would be even greater.

Since only a few species can be tested, a method for estimating the spread in species sensitivity is far more important than the estimation of chronic toxicity. We have virtually no ability to make any guess concerning the species range, except when sufficient data are available to make an extrapolation from our sample set. No theories as to the shape of such curves exist.

Progress in the area of comparative species sensitivity might yield a larger return than most areas of endeavor because such a capability would be as applicable to community judgments as to important species judgments.

(4) Residues, Tainting, Etc.

Some effects of exposure to chemicals cause no apparent harm to the population's viability, but lessen the value of individuals for man's use (e.g. formation of unacceptable residue and production of off-flavor).

Methods for measuring residues are well developed but usually measure only equilibrium, ignoring variable exposure and depuration. A larger deficiency is the frequent absence of data on what constitutes an unacceptable residue (i.e. a residue which impairs use). To obtain such data often requires expensive and lengthy tests on higher animals (such as primates) or predators (such as eagles). The prediction of direct accumulation from an ambient medium on an organism has been developed to a point of usefulness, but prediction from one trophic level to the next is not yet usable.

Methods for assessing off-flavor are insufficiently objective, and recent safety precautions prohibit use of test panels for evaluation. Methods development, especially in the area of prediction (as opposed to actual testing) needs to be improved.

b. Community Function Effects

In dealing with communities of organisms within an ecosystem, one of the primary needs is knowledge of the species interactions. The effects of perturbations on a system are reflected to a greater or lesser extent throughout the entire community. The extent to which we can measure these effects depends on our knowledge of these species interactions and the role of the species on the system function. Methods for assessing contaminants which cause immediate low-level response to stress are particularly important. Research must determine the sensitive indicators (including organismic, chemical, or biochemical indicators) which can act as rapid prognosticators for determination of effects on community function. Mechanisms of stress, resistance to stress, and recovery from stress are major areas of concern.

Community relationships involve complex interactions and processes between biotic and abiotic constituents. A ranking of the stress-sensitivity of major processes and their constituents may help to define the most sensitive indicators of stress. The major processes which contribute to community funtion and may be used to measure stress on a community are respiration, metabolic assimilation, primary productivity, growth and development, reproduction, behavior, and decomposition.

Organisms in any community produce gas and other byproducts as part of their life process (i.e. respiration). Quantitation of the levels at which the products are present during normal and perturbed states should provide an understanding of the relationships of the dose-response concept. To date, however, direct measurement of respiration appears to be among the least sensitive indicators of toxic organic stress. This may be due to the multiplicity of factors affecting differential analysis.

Since certain toxic organics are known to inhibit selectively macromolecular synthesis in some organisms, metabolic assimilation or biosynthesis could serve as indicators of stress effects on a known function.

Primary production at both higher and lower plant levels has been investigated by single species tests because of extensive herbicide usage. The photosynthesis process itself is not usually sensitive to stress, but the number of ways in which its efficiency can be reduced and the consequent drastic ecosystem repercussions suggest the need for particular attention.

At the community and ecosystem levels, growth must be considered to include genetic diversity and ecological succession. The community can accommodate some loss in diversity caused by stress; however, precaution must be taken that predominant species loss does not change the basic relationship and therefore function of that community.

Behavior is certainly central to the existence of any community of organisms, thus, behavior may be viewed as a community process. Mating and social behaviors, feeding motions, homing, phototropism, avoidance, and aggression are examples of a variety of responses at many trophic levels which may offer some measure of stress.

Information developed for the fate of chemicals may eventually allow us to determine where a chemical will ultimately reside in a community. Very little is known about the inhibition or disruption of the degradation process in nature by toxic organics. The fundamental ecological importance of these processes make them important as indicators of stress for community function. Nutrient cycles also may be included here. Since these cycles are necessary for the stable functioning of communities, they could serve as sensitive indicators of stress.

Bioaccumulation of chemicals by components of a natural community can lead to stress within the system or simple innocuous storage. Certain types of bioaccumulation are necessary for life processes (e.g. hydrocarbons in plankton), but accumulation of certain toxic chemicals by species within the system can lead to stress of a particular function. Also innocuous bioaccumulation, by some species, can through food chain magnification result in a stressful situation for some species of the community.

The exposure of potentially toxic chemicals to humans through their environment is a result of a complex web of physical, chemical, and biological processes. Prediction of hazard to man and the environment is possible only through integration of the discussed processes. Mathematical models provide a convenient tool for this purpose. Informational needs include sources, fate and transport, toxic effects, population dynamics, and environmental conditions. The development of chemical fate data and transport models is discussed under the section concerning estimating ambient concentrations. The kinetics of population dynamics, impact of toxic chemicals on communities, and bioaccumulation/bioconcentration data are discussed in this section. The integration of these data with exposure concentration models will provide ecosystem hazard prediction capability.

In the natural environment, the concentration of any substance varies in a continuous fashion. To model adequately the effect of the substance at any point in the environment, a continuous functional relationship between exposure concentration and the studied effect is necessary. From this relationship, a deterministic equation is derived for inclusion in the model. Needed toxicity information can be obtained from acute and chronic tests on important species. Population studies to quantify the effects of the potential toxicant on community structure and on predator-prey relationships as a function of the chemical concentration need to be developed. The effect of the chemical on rates of predation on prey populations and the consequences of severe reductions in certain classes of the community structure can then be quantitated.

The accumulation of toxic chemicals in various levels of the food chain is the result of both interaction with the surrounding environment and biomagnification through consumption. The major processes involved include uptake, assimilation, depuration, loss due to reproduction, and biotransformation. Each of these processes is complex, and all are intertwined. Research aimed at describing bioaccumulation should be as simple a representation as possible. Research needs will depend on the complexity necessary to describe the bioaccumulation process.

Tests for community function are not well developed, largely because in the past, emphasis has been placed on single species toxicity tests. There is a strong need to develop tests which will measure community responses to the effects of a toxicant on ecosystem processes. The most likely tests in this category are on simple microcosms and are designed to duplicate a process such as nutrient cycling or breakdown of leaf litter. Such tests are in planning stages, but still some time away from the final method and validation stages for standard use.

c. Interactions

Chemical substances are rarely found in their pure form, in uniform concentrations, or unmodified by natural physical, chemical, and biological factors in the environment. Natural environments may refer to either a perturbed state, i.e. man-made or modified environments such as the agro-ecosystem or urban communities, or to the unperturbed condition such as might be associated with a stream, a wetland, a forest, or a desert range land. Current scientific understanding of the interactions of chemical substances in a variable uncontrolled natural environment is primitive at best when compared to available knowledge of the effects pure chemical substances exhibit in laboratory tests. There are a few exceptions; for example, DDT has been well studied in both the laboratory and in the field and its ecological effects are relatively well understood. The basic understanding of how chemical substances affect human health directly is much better than the understanding of how these substances affect and interact with the natural environment.

Relatively little work has been done on the interactions of pollutants with the exception of the effort to define the synergistic actions of metal combinations. However, research is now underway to define the interactions of mixtures and toxicants with other environmental factors. Research has been initiated on toxicants present in complex waste effluents and the effect of the actions of various components. Tests have been conducted to determine the effect of toxicant-imposed stress on the susceptibility of salmonid fishes to naturally occurring diseases. These tests have demonstrated the effect of toxicant-imposed stress on the ability of salmonid fishes to adapt to salt water in their seaward migrations. They have also demonstrated that often suspected interactions may have vital consequences in the ecosystem. Such research on complex mixtures needs to be expanded in the future if any degree of confidence in "safe level" predictions is to be developed.

If EPA is to regulate chemical substances effectively and reasonably under TSCA, then the interactions of chemical substances introduced into the environment must be understood. The presently available knowledge of chemical risk and hazard assessment is derived through the use of simple laboratory test schemes and general action models which use pure chemical substances. The assessment of physical/chemical effects, biological effects, and fate in the natural environment remains largely unknown. The four principal areas of "interactions" research needed to relate laboratory test models with field realities are as follows: (1) the synergistic and antagonistic ecological effects of chemical substances; (2) multiple chemical exposure in the ecosystems; (3) complex chemical mixture effects on ecosystems; and (4) the physical, chemical, and biological factors affecting the action of chemical substances or chemical mixtures in the environment. This research should be conducted in all media (air, water, and land) and in the laboratory, and should be validated in the field. The results are expected to be vital in the assessment of long-term and cumulative damage to the ecosystem.

d. Abiotic Effects

Important abiotic effects of chemicals on the environment may include material damage, atmospheric modifications, acid precipitation, and aesthetic loss.

(1) Material Damage

The contribution of trace gaseous materials (which includes toxic compounds in the atmosphere) may have significant effects associated with damage to materials. However, a wealth of information does not exist on this subject. Thus, there is a need to define possible material damage due to chemicals either as single compounds or in association with other compounds.

(2) Atmospheric Modifications

Gaseous toxic substances and/or their reaction products which contain halogen atoms having sufficiently long lifetimes to be transported out of the troposphere into the stratosphere could result in depletion of the ozone layer. Research must recognize such long-term global effects associated with long-lived gaseous compounds.

(3) Acid Precipitation

Of particular interest is the effect of acid precipitation which results in changes in the acidity of lakes and streams. Outside the area of acid precipitation, few studies on the nature and concentrations of organic chemicals in rainfall within the United States have been conducted. Research is needed to measure the concentration of chemicals both in rainwater and the ambient air to elucidate the extent of removal of chemicals by precipitation. The validation of regional and continental models is important because of the impact of long-range transport of pollutants on acid rain problems.

(4) Aesthetic Loss

The possible result of aesthetic loss associated with visibility reduction from chemicals is virtually unknown. The main areas of research needs in aesthetic loss are associated with visibility reduction and odor.

e. Dose-Response Relationships

It has been known for some time that "dosage makes the difference" in regard to toxicity. The dose-response relationship can take many forms (linear, exponential, biphasic, etc.), but the application of that relationship is critical to the utilization of all the foregoing effects (single species and community) in hazard assessment. This relationship is assumed to allow the hazard assessment to be related to exposure assessment in order to determine risk. Primary information for these relationships is derived from acute, subchronic, and chronic exposures and measurements of the resultant effects. Since realistic exposures seldom take the form of the idealized continuous concentration and even exposure in the laboratory, the role of intermittent and stochastic exposure concentrations must be considered in developing the relationships. The methodology must be supported by valid statistical techniques and models which account for natural variations in response. Finally, the "population-at-risk" must be established through models which can connect the environmental concentration response surfaces to the response function with respect to concentration (considering other relevant factors) to provide a damage index or environmental impact (risk) assessment.

(1) Acute, Subchronic, and Chronic Exposures

Short-term exposure needs are being met in test method development to the extent that each assay procedure calls for output in the form of a dose-response relationship (e.g. EC-50). In some instances, for example terrestrial plants, problems are being experienced in obtaining such relationships.

The extent to which short-term exposures (acute and subchronic) permit chronic and intermittent exposure assessment needs to be determined. The relationship of chronicity of action for generic chemical classes (linearity of time x concentration *re* effect) must be known to determine dose-response relationships.

A stronger theroretical basis for understanding the relationships of exposure for different types of tests must be derived.

(2) Intermittent Exposures

Studies of the effects of intermittent, discontinuous, or stochastic exposures for significant effects are needed to supply a basis for realistic exposure-response relationships.

The relationship of chronicity of action for generic classes of chemical functions must be determined, and a means of ascertaining the theoretical relationships of different exposure patterns must be devised and applied.

(3) Statistical Methods and Models

Each test method must have appropriate statistical procedures for its use or derive such procedures for that application. Difficult areas include terrestrial plant responses, non-quantal responses (e.g. growth), and interactions between chemicals, species, and environmental factors in polyfactorial environmental tests.

New statistical models for dose-response application (and their computerized forms) are needed for the complex situations encountered in community studies and other systems functioning above the level of species.

The theoretical basis for statistical modeling and computer simulation of population/community interactions, with chemical concentration surfaces of exposure assessment model projections will be needed.

(4) Response Function or Damage Function Models

Simple cases which demonstrate the validity of linear dose-response models with respect to ambient concentrations under a variety of environmental conditions must be applied to show the usefulness of this approach in more complex exposures or responses. These simple models must be tested against actual situations in the field. More complex relationships must be examined which take into account environmental factors and population distributions of vulnerability with respect to age, class, or geographical distribution, so that estimates of impact can be made on a broader basis.

The final formulation of damage function or response function models, taking into account such factors as variable or intermittent exposure, interactions with other chemicals or environmental factors; and statistical models of response must be validated by explicit studies in the field (within a biome or watershed). These field studies must be on a large enough scale to justify generalization to large biomes or populations. The damage response model(s) must be examined for a large variety of chemicals and types of responses. When incorporated into computer simulations for hazard assessment, these models must be user-accessible and user-acceptable and of uniform language and format compatible with exposure assessment models.

3. Research Program

The ongoing toxics research program on ecological effects focuses primarily upon the development and verification of standard tests for defining environmental hazard to aquatic animals and plants. The repeatability of standard tests is being verified through a Round-Robin testing scheme, and several standard tests are near completion. These tests will be incorporated into testing guidelines and will be used by the Agency and industry in generating data for defining environmental hazards.

The development of structure/activity concepts for predicting the toxicity of chemicals is also a high priority of the program. Structure/activity concepts will be used as a screening tool for evaluating new chemicals. In order to observe plants and animals in a more realistic context, the development of laboratory ecosystems and microcosms is being emphasized. Microcosms are being developed to predict the effects and fates of toxic chemicals, as well as to test exposure models.

Research in the areas of food chain toxicology and behavioral toxicology is relatively new to the toxics program. Food chain research involves work on defining uptake, accumulation, and movement of chemicals in plant systems and in marine animals. Behavioral research is aimed at defining effects at the community level. Providing technical assistance to OTE on complex ecological problems is a major activity under this program.

The specifics of the research program include the continuation and initiation of work in the areas of single species tests, community level tests, interaction studies, abiotic studies, and dose-response relationships.

The development of tests for defining the toxicity of chemicals at community and system levels is lagging as compared to single species tests. Research is underway to design tests for aquatic and terrestrial communities. Microcosms are being developed as one of the tools to study the effect of chemicals on communities.

No immediate studies on interactions are underway, but the methodologic evaluation of several tests (germination, stress, ethylene, etc.) requires the testing of solvents and other materials used in suspending hydrophobic agents. These often have bioactivity and complicate interpretation of results.

Environmental factors in toxicologic response are an important part of the development of a support document for OTE and for application of the dose-response model to concentration models. In both community and single species testing, a variety of environmental factors (temperature, moisture, ventilation, etc.) are under study in microcosms and greenhouses. Quantitative relationships will be developed.

Extensive studies on the effects of acid precipitation are underway for crop loss estimates, soil community effects, and other significant factors under Air Ecology. Work on the effect of chemicals on ozone concentration in the stratosphere is also being carried out.

All dose-response assays under development are being established to provide a dose-response relationship which can be used in hazard assessment. Difficulties are being encountered with terrestrial plants because "death" is a much less clear endpoint for plants than for animals. Combinations of events and more complex decision trees are therefore being developed. New statistical and computer-based methods are being developed for plant responses to toxic substances. These will be incorporated into the support documents for the assays.

Each class of responses will require a set of tests and an evaluative model which will be used to provide a "response surface," which in turn will be used with the exposure assessment model "response surface" to determine the limits within which a vulnerable population might be adversely affected. These models will be developed at a later stage of toxicological testing.

Since ongoing ecological effects research is mainly devoted to the development of testing methodologes, many important areas are either addressed at a low level or ignored altogether. For example, our understanding of system level toxicity is inadequate, the synergetic and antagonistic properties of toxic chemicals and their role in defining hazard is not very well known, and little information is available on comparative toxicology as it relates to various ecological species.

These and other problems must be addressed in order to meet adequately the needs of TSCA.

Research Goals

- Continue development of several single species bioassays tests by a Round-Robin scheme in ORD Laboratory(ies) and contractor laboratories. These tests will be available for inclusion in testing guidelines and for use by the Agency and industry. (Highest Priority)
- Continue development of methods to evaluate acute, subacute, and chronic effects on organisms, including wild terrestrial vertebrates such as avian wildlife. (Highest Priority)
- Continue development of methods to evaluate acute and chronic effects and fate of chemical substances on benthic fauna. Tests include whole life cycle tests with benthic crustacean and tests for effects on reproduction and bioaccumulation in food-webs. (Highest Priority)
- Continue validation of a vertebrate cell assay. This assay is designed to detect carcinogens, mutagens, and teratogens in tissue, water, and sediment. (Highest Priority)
- Continue development of a toxicity/fate screening method to monitor disappearance of the parent compound with toxicity to an appropriate water or sediment organism. The fate screening will provide rates for adsorption, desorption, biodegradation, and hydrolysis in sterile and nonsterile systems. The toxicity test is designed to monitor toxic metabolites. (Highest Priority)
- Develop and conduct interlaboratory testing on various species for seed germination and stress. Ethylene stress tests have been or will be completed within the year. These tests provide a spectrum of important agronomic species regarding a critical phase of early development and growth. For life cycle studies, the Arabidopsis spp. have been identified by Air Ecology as candidates for short-term (28-day) tests from seed-to-seed. A life cycle test for Duck weed is nearing completion. (Highest Priority)

- Evaluate seedling root elongation as a more sensitive and reliable response to phytotoxicity to the young plant. This method will be used to define the phytotoxicity of chemicals. (Higher Priority)

- Continue development of a screening method based on the Microtox microbial bioassay using photobacteria. This method involves inhibition of bioluminescence as a function of toxicant concentration. At present, this method is being refined to increase the sensitivity. If it appears promising, then the next step will be to determine its repeatability via Round-Robin testing. (Higher Priority)

- Continue development of structure/activity concepts to predict toxicity of chemicals. The structure/activity concept is based on the correlation of toxicity with the octanol/water partition coefficient and structural characteristics of a series of chemicals in a homologous series. To date, toxicity, partition coefficients, and bioenergetic parameters are being collected to be used in structure/activity development. This concept, once developed, will be used as a screening tool for evaluating the toxicity of new chemicals under Section (5) of TSCA. (Highest Priority)

- Continue several projets already underway to study behavioral interactions at species and community levels in the presence of toxicants. Qualitative determinations of effects between known toxicants and other chemicals are being quantified. (Highest Priority)

- Conduct studies on the effects of chemicals on primary productivity. (Highest Priority)

- Continue studies on decomposition and recycling processes in microcosms as a part of efforts to develop a means for using standard microbial studies in holistic methods. These systems also will be involved in food chain transformation. Continue studies on stability resistance and resilience in soil core and soil-litter microcosms. (Highest Priority)

- Continue development of methods to determine the effects of toxicants on ecosystem processes in laboratory aquatic microcosms. (Highest Priority)

- Continue to assess the food chain effects of water borne toxicants. The work involves survey of field situations in order to determine key species and interactions affecting food chain processes. These will later be studied in laboratory microcosms. These studies will provide ecological effects data and the extent of biotransformation, bioaccumulation, transport, and retention of toxic chemicals through the food chain. Biological fate data will be combined with ecological effects data in order to assess hazard to humans. (Highest Priority)

- Continue development of nitrogen flux methods to define transport of nitrogen in soil-plant-animal systems. Selected tests are anticipated to reveal system dysfunction indicative of stress from a toxic chemical. Attempts will be made to correlate individual in vitro assays and the disruption of nitrogen flux. (Higher Priority)

- Continue to link ecological effects data with human health effects data as related to food chain problems. (Higher Priority)

Future Research

- Continue development of single species tests and accelerate the development of testing protocols for community and system level responses. Emphasis also will be placed on multiple species tests. (Highest Priority)

- Expand the work on food chain toxicology and behavorial toxicology. (Highest Priority)

- Initiate work on comparative toxicology. This area is important since it may lead to identification of indicator species as related to evaluating toxic chemicals' effects on humans. (Highest Priority)

- Continue ecosystem research with emphasis on identifying important processes, ecological effects, and selected species as indicators of ecosystem stress. Research also will include work on a better understanding of the ability of ecosystems to withstand contaminant stress. (Higher Priority)

The following additional research areas are strongly recommended:

- Initiate field validation to assess the capability of all existing and prospective testing protocols to predict responses in various real world environments. (Highest Priority)
- Initiate development of pathobiological methods for possible incorporation into predictive and descriptive models for structural and functional effects and as a documentary tool in chronic test protocols and in tier testing schemes. (Highest Priority)

SECTION 6

MONITORING RESEARCH STRATEGY

I. OVERVIEW

Toxic substances can enter the environment at the source of production, and/or during product use, transport, and disposal. Monitoring is used to help identify which of these entry points, if any, should be controlled and to determine the extent of control needed. Once a control strategy is adopted, monitoring is used for enforcement. Finally, monitoring is used to assess the effectivenesss of the regulatory strategy chosen.

In regard to identification or problem definition monitoring, TSCA is to be invoked as umbrella legislation in only those cases where other environmental legislation, such as the Air or Water Quality Acts, is not appropriate. Accordingly, a considerable amount of monitoring data relevant to TSCA will be collected by monitoring programs supported by other environmental legislation. Further, much of the data collected under TSCA will be provided by industry in response to specific testing protocols for the regulation of chemicals. Thus, the problem definition monitoring effort under TSCA should be limited to filling in the data gaps for existing chemicals in cases where industry is not required to submit data and/or data are not available from other regulatory programs. In all cases, the Monitoring Research Program manual under TSCA will be consistent with the Integrated Toxic Monitoring Strategy currently being developed by the Agency.

A. RESEARCH PRIORITIES

During the initial implementation of TSCA, the focus of the research program in the monitoring area will be directed towards activities of a technical support nature. Effort will be concentrated on developing and validating field collection and analytical methodologies needed to:

- Fill in the gaps in the data base on existing chemicals.
- Assist in the development of appropriate testing protocols and environmental and exposure assessment models.
- Develop suitable guidelines/procedures for the validation and verification of predictive models for future assessment activities.
- Enforce existing and planned TSCA control regulations.
- Assure that appropriate Quality Assurance guidelines and protocols are developed and implemented for all monitoring activities.

For all of the above efforts, the underlying philosophy is to deliver the research product in such a form that eventually much of the routine collection of data can be performed extramurally.

In addition, the research capability will be used to assist the Regions where appropriate. From a Regional perspective, TSCA's testing and evaluation monitoring activity is focused on the areas of enforcement and problem identification/evaluation. Regional Offices are required to respond to a variety of situations involving potentially toxic substances. In order to evaluate the hazard involved in these situations and the need for control action, monitoring activity is often necessary. Where the appropriate surveillance and analysis capability exists, this monitoring can be performed by the Regional Offices themselves. Often, however, resource limitations prevent extensive monitoring, and assistance is needed from ORD and/or other Headquarters' program offices. Monitoring assistance could be in the form of direct analytical support or contractor support. By close coordination of Headquarters contract and direct monitoring efforts and Regional Office requirements, monitoring activities can serve multiple needs.

B. IMPLEMENTING STRUCTURE

The TSCA implementation program falls under the planning purview of the Office of Monitoring and Technical Support (OMTS). The majority of the monitoring and field related activities are implemented by the Environmental Monitoring Systems Laboratory (EMSL) at Research Triangle Park, North Carolina, and Las Vegas, Nevada. The Environmental Monitoring and Support Laboratory at Cincinnati, Ohio, provides relevant support in the water area.

Advanced Methodology Development activities are implemented by the Environmental Research Laboratory (ERL) at Athens, Georgia, and the Environmental Sciences Research Laboratory (ESRL) at Research Triangle Park, North Carolina.

C. PROGRAM STRUCTURE

The monitoring program can be divided into two major subactivities; research in support of Testing and Assessment and research in support of Chemical Specifics. These categories correspond to the two major responsibilities under TSCA, namely: (1) the development of suitable tests and assessment methods for industry to follow in submitting the data required for existing chemicals or requested for new chemicals; and (2) the development of analytical methods and associated Quality Assurance for the regulation of specific chemicals. The testing and assessment program is further broken down into: (a) research required to develop laboratory analytical methods, utilizing both chemical/physical characteristics and biological reactions; and (b) research to develop and apply suitable field monitoring methodology. The chemical specific program is devoted to research on specific products identified by OPTS as possible candidates for regulation.

II. TESTING AND ASSESSMENT

In the testing and assessment area, the primary goal of the monitoring program is to support the assessment function. Except for peripheral assistance from the monitoring program, the test protocols for industry will be developed under the health and environmental programs.

Monitoring research in support of the assessment responsibility is aimed at identifying toxics, determining the extent to which they are currently present in the environment, and assessing the effectiveness of TSCA regulations in controlling them. The former information is needed to help establish priorities for addressing the numerous existing chemicals which pose possible hazards to man or the environment. The latter category involves developing suitable monitoring techniques to assess whether the test results required from industry do, in fact, effectively control the release of hazardous chemicals into the environment.

Research to meet these objectives falls largely into two areas; the analytical or laboratory methods development program and field monitoring.

Methods development is a broad, all-inclusive area which includes development of: (1) general and specific analytical methods for pollutants (on a matrix-specific basis); (2) continuous and grab sampling methodologies by matrix, media, and pollutants; (3) QC/QA techniques which are most cost-effective based on the eventual use of the data; and (4) the expansion of analytical methods, allowing a broader range of pollutants to be identified and quantified by a single method.

The second major activity supporting the testing and assessment program is field monitoring. Field monitoring studies will be conducted in order to apply, assess, and refine newly developed monitoring techniques, to obtain data needed for validating exposure assessment models, and to help define the extent to which toxics are present in the environment. Additionally, field studies will be conducted at industrial sites identified by OPTS to collect data needed to validate environmental system models for assessing pollutant exposure. Included in these models are fenceline monitoring methods for air and multi-media sampling methodologies, for example, environmental field sampling methodologies useful for collecting data needed for exposure assessments. The intent of these methodologies is to develop standardized sampling protocols for specific pollutants or classes of pollutants in all media.

OPTS has established the following priorities for monitoring research:

- Develop analytical methods in the ppb and ppt range for a range of chemical classes.
- Refine existing analytical methods.
- Develop non-invasive human sampling techniques.
- Collect base-line data for tissue bank establishment refinement.
- Characterize the transport and fate mechanisms of a range of chemical classes.
- Develop and operate QA/QC activities to support the above.
- Provide expert technical assistance as required.

A. METHODOLOGY DEVELOPMENT AND MEASUREMENT SYSTEM RESEARCH

A major area of research activity in the monitoring area is concerned with the development of methodologies for identifying and quantifying new and existing toxic chemicals or their major degradation products in biological matrices, in air, water, soil and sediments, and in commercial products. These toxicants vary widely in their chemical characteristics and detectability and without doubt will continue to present detection and analytical complexities well beyond the foreseeable future. Therefore, it is important that a vigorous, broadly-based program in the analytical chemistry of toxic substances be pursued. Thousands of organic and inorganic chemicals in the broadest possible matrices will require measurement by standardized methods with good quality control. This monumental task will involve great expense; thus, cost-effectiveness must be an essential objective of the methodology development and measurement system research program.

1. Chemical/Physical Measurement Capability

(a) Background and Status

At the present time, our knowledge of the kinds and quantities of organic chemicals present in the environment, many of which may be toxic, is limited. Therefore, it is necessary to develop methods that are broadly applicable to the wide varieties of chemical properties they represent.

The methods currently available for the collection and analysis of toxic organics have not been adequately validated. In addition, collection and analysis methods do not exist for many toxic organics. Different collection systems are needed for different media as well as for different chemicals. Similarly, laboratory analysis techniques for samples must be appropriate to the volatility and chemical nature of the toxic organics collected. Various types of gas chromatographic separation columns must be evaluated to determine their suitability for the separation of toxic organics. Lastly, the detector system for identifying individual toxic organics after separation must also be evaluated.

(1) Sampling Methodology and Preparation

It is important to keep in mind that regardless of the analytical technique chosen, the data obtained can be no better than the sample collected. Proper sample collection is critical for a good analysis.

In air, gaseous air samples are collected by a variety of techniques, such as solid sorbents, plastic bags, cryogenic traps, and evacuated containers. Particulate samples are collected by various types of filters, impactors, and electrostatic precipitators. No one sample collection method is universally valid for all chemical species. Therefore, a variety of sampling techniques must be used. Tenax, for example, shows low capacity for hydrocarbons less than C_6 and low recovery efficiency for high boiling compounds. The validity of sampling methods is affected to a greater or lesser extent by such factors as collection efficiency, desorption efficiency, shelf life, sample capacity, chemical interactions, volatilization, and condensation of chemical species. The various sample collection methods in use today have not been fully evaluated or optimized for these variables. Tenax, as well as other collection techniques for both gases and particulates, need to be evaluated for interferences arising from reactions with SO_2, O_3, and NO_2, and other reactive components in the atmosphere. Volatilization and condensation of chemical species on particular filters must be evaluated to determine the extent to which the phase of a chemical species may be altered during sampling. Methods for transferring and interfacing air samples to the particular analytical instrument being employed need to be optimized. The factors involved include sample concentration, sample volume, and removal of interfering compounds.

In the area of sediment analysis, work is only recently being initiated. A difficult task in this area is the development of separation techniques which allow accurate identification and quantification of both volatile and involatile organics.

(2) Analytical Instrumentation

The state-of-the-art for the analysis of toxic and/or hazardous organic compounds generally involves the analytical techniques listed below:

- Gas chromatography (GC) with selective detectors
    - Mass Spectrometry (MS)
    - Flame Ionization Detector (FID)
    - Electron Capture Detector (ECD)
    - Fourier-Transform Infra-Red (FTIR)
    - Ultra Violet (UV)
- High Pressure Liquid Chromatography (HPLC) with selective detectors
    - Ultra-Violet (UV)
    - Refractive Index (RI)
    - Fluorescence
    - Mass Spectrometry (MS)
    - Droplet Electrification (prototype)
- Visible, UV, and IR spectrum measurements
- Electrochemical techniques

All of these techniques have been and are being used successfully for the analysis of organic compounds. Many are useful for both screening or qualitative determinations.

(a) Gas Chromatography with Selective Detectors

Gas chromatography coupled with one or more detectors is frequently applied in the measurement of organic pollutants.

Gas chromatography/mass spectrometry (GC/MS) is the most widely used technique because of its capability for identification of specific pollutants of interest in complex mixtures. Recently, the GC/MS approach has been useful in determining the 129 priority pollutants in industrial effluents and in screening chemicals present in atmospheric samples. Effort must now be focused on extending this tool to analyze for organics in soils and sediments. Although the mass spectrometer is a highly versatile detector, identification based on gas chromatographic retention times and mass spectral data sometimes may not be definitive. In these cases, Fourier-Transform Infra-Red (FTIR) Spectroscopy provides the additional data for definitive identification. GC/MS systems are costly; moreover, accurate identification and measurement of unresolved chromatographic peaks require time-consuming manual data analysis methods. Samples of certain classes of organic compounds require only limited analysis. Thus, the high cost and complexity of GC/MS make it imperative that simpler and less costly methods such as GC and HPLC be developed for these compounds.

To date, GC/FTIR has been used mainly for identification of the so-called volatile organic compounds in simple matrices. The term volatile organic compounds is applied to those compounds that are separated, can be separated, or can be caused (by derivatization) to separate by gas chromatography. Although the data base for the identification of volatile organics by mass spectrometry for some media is adequate, the corresponding data base for vapor phase infra-red spectroscopy is only a fraction of that required.

Fourier-Transform Infra-Red spectrometry has been employed to study organic species in photochemical smog reaction. Ultraviolet (UV) and infra-red (IR) spectra and fluorescence have been used to identify atmospheric organics. Work is underway to apply the FTIR technique in the water and sediment area.

(b) High Pressure Liquid Chromatograph (HPLC) with Selected Detectors

The non-volatile organics, including refractory organics, comprise a large fraction of the organic compounds whose occurrence for the most part has not been well documented or investigated. HPLC advances should assist in this area.

Some success has been achieved in interfacing a liquid chromatograph with a mass spectrometer in the analysis of a few compounds. A HPLC/MS instrument (Varian) is commercially available but has not as yet been proven to be a useful analytical tool. Since the state-of-the-art has not permitted the routine coupling of a liquid chromatograph with a mass spectrometer (as can readily be accomplished with a gas chromatograph), broad scale survey type analyses have not been carried out. Therefore, a much more intensive effort is needed in this area.

Although the new prototype universal HPLC detector based on droplet electrification is feasible, it is still in the process of development and is not ready for general use in the scientific community.

Methods for analyzing the non-volatile organics absorbed on sediments must also be developed.

The interfacing of liquid chromatographs with molecular spectroscopic techniques is also needed in order to provide the same positive identification that is required for gas chromatography.

(c) Other Techniques

It appears that the chromatographic/mass spectrometry or FTIR approach is the most cost-effective for monitoring a large number and variety of compounds. However, in some cases and in particular for the non-volatile compounds, group-specific detectors which may depend on electrochemical properties or rapid screening UV absorption may be desirable. In addition, direct mass spectra analysis of environmental samples without preseparation of components by GC is needed to simplify and accelerate the analytical process and to avoid the problems and limitations encountered in GC analysis.

The toxic inorganic elements are determined by multi-element techniques such as inductively coupled plasma emission or X-ray spectroscopy. Of these two techniques, plasma emission spectroscopy is more suited to the analysis of solids. Other approaches may be taken in plasma emission spectroscopy which allow a simultaneous multi-element analysis on solids, tissues, etc., and which require no sample preparation. These approaches should be investigated.

It is well recognized that the oxidation state of a metal ion is critical to its toxicity. Furthermore, complexing agents, such as humic acids, may be a critical factor in the transport of certain metallic ions. The toxic anions, arsenate, selenate, etc., have received very little attention, yet ion chromatographic techniques have been shown to be useful in determining such species.

An electrochemical technique called potential sweep cyclic voltammetry has been studied for sulfides and amines. Ion chromatography is also being studied for the analysis of organic acids and aromatic amines.

b. Research Strategy

As indicated earlier, we will rely mainly on methods being developed through media programs set up primarily under the Air and Water Quality Acts. TSCA resources will be used to study areas which are not addressed under other media, or which are addressed on a time frame inconsistent with TSCA requirements. Our present program addresses only the most immediate problems and highest priorities of TSCA. Existing chemical screening methodologies will be examined to streamline operations and reduce costs per sample for specific chemicals or classes of chemicals as specified by OPTS. Automation and streamlining of equipment are also included. We expect that this directly responsive "reaction" mode will continue for several years, until instrumentation and analytical techniques developed for this and other programs broaden sufficiently to allow detection of almost any type of chemical residue in almost any medium and matrix.

c. Research Program

Immediate Research Goals

- Develop new detector for high pressure liquid chromatography using charged electrostatic droplets. Feasibility will be demonstrated in FY-79; emphasis in FY-80 will be on interface of detector with HPLC and on improving sensitivity and resolution.

- Continue program to develop system for collection, characterization, and quantification of volatile organic compounds in ambient air environments using GC/MS. Emphasis in FY-80 will focus on the extent, if any, of artifact formation with Tenax cartridges and the development of improved computer techniques for analysis of GC/MS data.

- Investigate methods for separation, characterization, and quantification of toxic chemicals bound to sediments. Effort in FY-80 will focus on separating volatile organics from sediments in quantitative fashion.

- Conduct research to optimize methods for collection of PCBs in ambient air. Solid sorbent collection techniques will be developed and evaluated for the selective collection of halogenated biphenyls.

- Develop simplified, quick analysis of methods for sampling particular classes of toxic compounds in ambient air, using for example, GC and HPLC with class optimized columns and detectors. Optimize sample collection and transfer techniques with Tenax cartridges.

- Conduct research to apply and streamline a combined GC/FTIR system. Tests to determine sensitivity of the system for dioxin measurements will be made. Upon completion of this phase, additional studies will be performed to determine the feasibility of using a manifold of gas chromatographs to provide "production type" dioxin analyses.

- Conduct a problem definition study to determine the state-of-the-art for routine multi-element analysis of environmental samples. An objective of the study will be to evaluate various techniques for conducting multi-elemental analysis of samples without sample pretreatment.

- Maintain MSS Library access for water spectra.

Intermediate and Long-Range Research Goals

- Continue program to collect, characterize, and quantify volatile organic compounds in ambient air. Effort will focus on:
  - determining *in situ* reactions on Tenax GC Cartridges
  - investigating alternative sorbent materials for Tenax
  - further development of capillary technology
  - extensive field validation of field collection methodology developed under this effort
- Assess the effects of particle/vapor interaction on atmospheric sampling for vaporous toxic compounds. A gas particle separator for the collection of gaseous atmospheric samples will be designed for the separation of particles of 0.1 micrometer and above. Compounds to be assessed include high molecular aliphatic hydrocarbons polyaromatic hydrocarbons including benzo(a)pyrene, and phthalic acid esters.
- Continue program to develop methodology for measuring organics in sediments.
- Conduct research to optimize methods for chromatographic separations of organic pollutants in complex mixtures. Techniques employing blended chromatographic phases and modified carrier gases to improve separation will be examined.

2. Methods for Measuring Organics in Biological Matrices

a. Background and Status

The availability of analytical methods for identification and quantification of toxic chemicals in biological matrices is critical to the implementation of TSCA, both from the standpoint of estimating exposure and as a monitoring tool.

In the case of estimating exposure, data are obtained either by analysis of biological samples or by using predictive models. Since predictive models must be validated from available data, both methods depend upon the availability of a credible measurement method. Measurement methodology is also critical in carrying out certain fate and effects tests needed for estimating the hazard of toxic chemicals. Finally, biological matrices such as plants or marine animals are major components of food chain models.

Biological organisms and biological media offer unique advantages in monitoring for toxic chemicals in the environment and at the same time present a complex set of problems inherent in their use. Two major advantages are that: (1) detection of a compound in a target organism or a biological medium is a direct confirmation of exposure which may reduce the need for extended ambient monitoring to arrive at the same conclusion; and (2) biological systems have been in place for long periods of time and therefore offer an opportunity for retrospective assessments of pollutant levels which is extremely important when attempting to determine the cause of such effects as cancers occurring 20 to 30 years after exposure.

The present state-of-the-art for measuring chemicals in a biological matrix is inadequate. Methodologies for assessing exposure concentrations of toxics in biological matrices such as plants and animals is also poorly developed.

Research is needed to adapt exposure methodologies to monitoring. Biological monitoring includes using the biological media as a collector and as a sensor. When used as a collector, additional sample preparation and analysis are required to determine the presence and concentration of a chemical. The biological matrix itself can produce major interferences in present analytical techniques and therefore usually requires careful and complex extraction and separation procedures prior to analysis. This is probably the most serious disadvantage to using biological media as collectors. On the other hand, when using biological organisms as sensors (such as tradescantia, AMES, and radio-immunoassay), the detection of a compound is related to the observation of a change in the organism or media and no special extraction or analysis is necessarily required. However, the results are only qualitative and the techniques still may require large initial investments to develop sensitive strains of organisms responsive to compounds of concern.

Research needs to be conducted to develop a series of simple false/positive biological monitoring methods for specific pollutants. For example, the state-of-the-art for analyzing dioxin is minimal and confined to: (1) gas chromatography combined with low or medium resolution mass spectrometry; and (2) radio-immunoassay techniques. Although these analytical methods are excellent for detecting dioxin in environmental samples, the relative cost, the complexity of GC/MS instrumentation, the preparation of antibodies from dioxin derivatives, etc., make such techniques accessible to only a limited number of laboratories. Rapid and inexpensive biomonitoring methods are needed to initially screen for the presence of dioxin and other toxics in the environment.

b. Research Strategy

Emphasis will be placed on developing rapid biological screening methods for those chemicals of immediate regulatory and enforcement concern. Efforts will focus on applying bacterial and/or enzymatic reactions to specific chemicals or classes of chemicals to produce non-extractive, qualitative chemical analyses techniques. In addition, a biological methodology will be developed for the identification and quantification of specific pollutants. First priority will be given to the development of a suitable method for testing dioxin.

c. Research Program

Immediate Research Goals

- Determine the feasibility of developing a biomonitoring microbial test system for dioxin. This approach will include screening strains of microorganisms for both "specificity" and "sensitivity" to dioxin.

Intermediate and Long-Range Research Goals

- Continue development of biological monitoring methods for pollutants specified by OPTS.

B. FIELD COLLECTION METHODOLOGY AND MONITORING ACTIVITIES

1. Background and Status

In addition to analytical methods development and laboratory advances, field studies are needed to develop and/or apply improved techniques for collecting representative data in field situations. Whenever possible, field methodology studies will be conducted to expand the data base for pollutants of specific interest to TSCA. Monitoring studies will also be conducted in support of chemical characterization, transport and fate studies, and assessment activities.

Current effort in the area of field methodologies falls mainly in two categories: (1) the development and validation of field methods in support of assessing the extent of toxics present in air; and (2) studies to develop and validate multi-media field techniques. In addition, the monitoring effort is supplemented by the work being carried out under the Public Health Initiative which is funded under the Environmental and Health Sections.

a. Field Studies in Support of Assessing the Extent to Which Toxics are Present in Air

Field studies of toxics in air are needed to determine the impact of selected emission sources on air quality. This information is used in risk assessment models, which provide scientific support of regulatory actions. Methods used in developing basic intelligence for a regulatory standard and those used to determine the effectiveness of the standard must have a known precision and accuracy as well as sufficient sensitivity and selectivity. For these reasons, it is important that methods used for assessing the extent to which toxics are present in air are initially evaluated under the conditions of use, and that procedures for sampling and analysis be carefully documented, including provisions for quality assurance. In ambient air assessment, ancillary measurements of meteorological conditions are also needed to demonstrate the representativeness of the samples collected. In short, before a method is used for assessing the extent to which toxics are present in air, it is first examined in the laboratory and in the field to determine its validity. The method is then improved if necessary, and detailed written procedures are prepared. During the course of the field study, a quality assurance plan is implemented to assure and document the precision and accuracy of the data reported.

For the past two years, the field monitoring effort has focused on developing field collection and sample preparation procedures for applying GC/MS to screen for some 70 to 100 organic compounds in air samples collected at various industrial facilities. Air sampling has been conducted in Lake Charles and New Orleans, Louisiana; Beaumont and Houston, Texas, Niagara and Buffalo, New York; and Newark and East Rutherford, New Jersey.

Other techniques need to be evaluated for the measurement of polar organic compounds in ambient air and of organics in the molecular weight range of below C_4 and above C_{20}. Avenues of approach include use of other polymeric sorbents, vacuum thermal desorption or solvent extraction of Tenax, and cryogenic sampling. Also, the current Tenax GC/MS technique needs to be optimized for quantitative analysis of selected high priority toxic substances. The technique as currently applied is qualitative or semiquantitative at best and is used for broad-spectrum identification of volatile organic compounds in air.

OPTS is currently interested in chemicals used by the dyestuff and textile industries, including benzidine, substituted benzidine, and dyestuffs derived from benzidine. High molecular weight organometallics produced or used by these industries are also of interest. Determination of these substances in ambient air will require methodologies different from the GC/MS techniques used for volatile organics. Particulate sampling devices, including low and high volume samples and high pressure liquid chromatography, are the most promising techniques presently available.

Research is also needed to develop improved methods for tracing the source of toxic pollutants in air. When toxic materials are present in atmospheric particulates in amounts which represent an unacceptable health risk, it is important to identify the sources of these pollutants so that appropriate control measures can be taken. By assessing the contribution of individual emission source categories to pollutant concentrations in the atmosphere, control strategies can be selectively directed toward those sources found to contribute significantly to the health risk.

Research is needed to determine the feasibility of developing data analysis methods capable of relating toxic organic pollutants occurring in atmospheric particulates (or in the gaseous phase) to their orgins. Some success has already been achieved with source apportionment of chemical elements found in particulate air samples and also with certain stable gaseous components of the atmosphere. Some factors, such as inplant variability of emissions, similarity of emissions from a given class of sources, meteorology, atmospheric transformation of pollutants, particle size distribution and chemical composition, relationships between organic particulates, organic gases, chemical elements, and the quality and availability of required data still need to be investigated.

b. Multi-media Field Activities

TSCA holds a unique place in the scope of EPA's responsibility because of its charter to approach pollution problems on a multi-media basis. OPTS is currently evaluating various models capable of predicting the transport and fate of pollutants and human exposure to pollutants. These models will be used to assess risks associated with the manufacture and use of selected chemicals. Before these models can be used they must be validated. Validation entails comparing model predictions with actual field data and determining model precision or accuracy. Therefore, it is very important that the field data be at least as precise as the resolution capability of the model. Guideline documents need to be developed on how to collect field data for the purpose of model validation.

c. Public Health Initiative

A major objective of the Public Health Initiative, discussed in greater detail under the Environmental Program, is the development of exposure monitoring methodology to permit the systematic measurement of actual exposure to individuals to a select set of chemicals by all major routes of exposure.

An intensive exposure monitoring field study will be carried out in FY-80 to provide the first definitive set of integrated exposure measurements of chlorinated hydrocarbons for a large sample of population. The study should also result in a series of protocols for sampling design and exposure monitoring methods and measurements useful for further analysis of exposure to other pollutants.

Future monitoring work under the Public Health Initiative will be directed toward: (1) instrumentation and methods development for chemical, physical, and physiological monitoring; and (2) field testing and validation of work being carried out under the Transport and Fate portion of the Public Health Initiative.

2. Research Strategy

Field studies will be conducted to develop suitable guidelines or protocols for the collection of data both in ambient air and in multimedia situations. The primary objective of these studies will be to develop methodology (or "how to manuals") that can be transferred to the private sector, so that in the future monitoring activities can be routinely conducted on a contract basis. As a secondary objective, the studies will be designed to collect data on pollutants of specific interest to OPTS, which can be used to establish a monitoring data bank on these substances. The pollutants selected and the models which will be validated first will depend on the requirements of the testing and assessment program of OPTS.

3. Research Program

Immediate Research Goals

- Complete analysis of air samples collected at the fenceline of chemical plants using a GC/MS organic screening technique. Compounds identified by this technique fall in the range of C_4 to C_{20} carbon numbers.

- Adapt field sampling techniques and analytical methods for use in determining atmospheric levels of pollutants of concern to OPTS relatable to textile and pigment manufacturer. Compounds of concern include azobenzene, 4-aminobiphenyl, benzidine, and 3,3' dichlorobenzidine.

- Develop stream sampling procedures that can be used for model validation. Provide field data on several toxic substances that can also be used for further model validation. The study will entail reviewing the models OPTS is considering, selecting a stream and pollutants, field sampling over a one-year period, analyzing the data, and writing reports.

- Conduct an exposure monitoring field study as part of the Public Health Initiative. Integrated exposure measurements for chlorinated hydrocarbons will be taken for a large sample of population. Protocols will be developed for sampling of design and exposure monitoring methods. Personal monitors for exposure measurements will be tested.

III. CHEMICAL SPECIFIC CONCERNS

A. BACKGROUND AND STATUS

The chemical specific area is concerned with specific chemicals which have been identified as requiring TSCA regulations of some type, or for which additional chemical specific monitoring information beyond the general laboratory tests prescribed under Section 4 is required. In the latter case, research will be required to provide chemical specific monitoring programs to be included in test rules for industry to follow in providing the required monitoring data on specific chemicals.

Enforcement of TSCA regulations, especially those promulgated under Section 6, requires the development of standard analytical methods for regulated substances in the specific media that will be encountered. Analytical methodology here includes all activities associated with sample collection, preparation, analysis, and quality assurance provision. Vigorous quality assurance is essential to assure the validity of analytical data generated. Accordingly, quality assurance considerations should commence as soon as the Agency decides to take a control action. This will assure that QA considerations are fully applicable when the regulations become effective.

Since in most cases the Regional Offices have primary responsibility with respect to TSCA compliance monitoring and associated enforcement, regional TSCA needs in the chemical specific area are identical to those of the Office of Enforcement.

B. RESEARCH STRATEGY

Top priority is being given to the development and improvement of methods for chemicals already under regulation by the Agency.

At present, there is an immediate need for analytical methods for PCBs in oil. Compliance monitoring with respect to final PCB manufacturing, processing, distribution in commerce, and usage regulations effective July 2, 1979, require PCB analysis in mineral oil and waste oils. Additional analytical methods are needed for PCBs which appear as impurities or byproducts in the production of chemical substances and the monochlorinated biphenyl species. In this area the methods should either be developed by EPA or validated by EPA if they are developed by industry.

Next in order of priority are chemicals for which regulatory options are currently under development. Table 6-5 is a list of chemicals that the Interagency Testing Committee has identified as potentially hazardous to human health and the environment. Some 21 substances have been identified in the four reports issued to date. The chemicals listed in Table 1 have been identified for early action.

C. RESEARCH PROGRAM

Immediate Research Goals

- Direct research toward developing methods to identify trace organics in various commercial products. In FY-80, effort will focus on determination of trace levels of PCBs in an oil matrix. Various separation techniques such as solvent extraction ion exchange, selective absorption, and volatilization will be evaluated. These impurities will subsequently be separated for identification and measurement by the most applicable technique (GC/MS, HPLC/MS, GC/FTIR, or Ramon Spectroscopy).
- Conduct research to examine the control of asbestos and freon from automobiles. Ambient measurement methods will be used to determine the effectiveness of wet vacuum and other brake drum cleaning methods for the control of the asbestos-containing debris from worn brake lining, and to determine the effectiveness of techniques for recovering freon from the air conditioning systems of junked cars. The effectiveness of non-freon substitutes in automobiles' air conditioning systems will also be evaluated.

Intermediate and Long-Range Goals

- Identify and measure bituminous road surface emissions in atmospheric samples. Sampling techniques will be devised to collect roadway air samples enriched in emissions resulting from frictional forces between tires and bituminous road surfaces. Gaseous and particulate samples will be analyzed to determine the nature and amounts of toxic organic materials in the emissions. The toxic components shall be related to the composition of the tires and pavements tested.

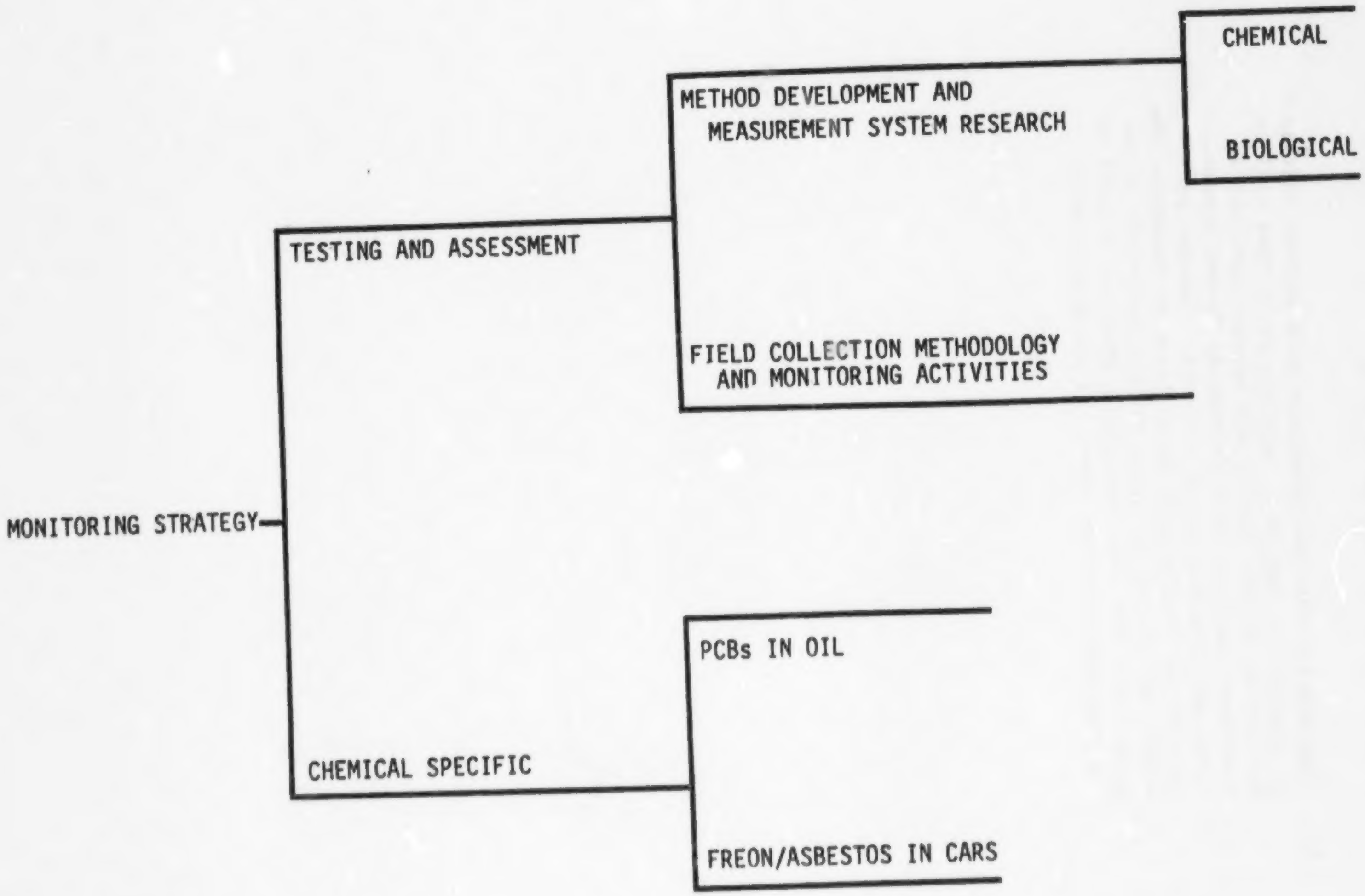

MONITORING STRATEGY
TESTING AND ASSESSMENT
METHOD DEVELOPMENT AND MEASUREMENT SYSTEM RESEARCH
CHEMICAL
BIOLOGICAL
FIELD COLLECTION METHODOLOGY AND MONITORING ACTIVITIES
CHEMICAL SPECIFIC
PCBs IN OIL
FREON/ASBESTOS IN CARS

FIGURE 6-1. MONITORING STRATEGY FLOW DIAGRAM

TABLE 6-1. THE TSCA SECTION 4(e) PRIORITY LIST

COMPOUND	DESIGNATED FOR ACTION BY: *
Acetonitrile	April 1980
Acrylamide	April 1979
Alkyl epoxides	(October 1978)
Alkyl phthalates	(October 1978)
Aniline and bromo-, chloro-, and/or nitroanilines	April 1980
Antimony (metal)	April 1980
Antimony sulfide	April 1980
Antimony trioxide	April 1980
Aryl phosphates	April 1979
Chlorinated benzenes, mono- and di-	(October 1978)
Chlorinated benzenes, tri-, tetra- and penta-	October 1979
Chlorinated naphthalenes	April 1979
Chlorinated paraffins	(October 1978)
Chloromethane	(October 1978)
Cresols	(October 1978)
Dichloromethane	April 1979
1,2-Dichloropropane	October 1979
Cyclohexanone	April 1980
Glycidol and its derivatives	October 1979
Halogenated alkyl epoxides	April 1979
Hexachloro-1,3-butadiene	(October 1978)
Hexachlorocyclopentadiene	April 1980
Hydroquinone	April 1980
Isophorone	April 1980
Mesityl oxide	April 1980
4,4-Methylenedianiline	April 1980
Methyl ethyl ketone	April 1980
Methyl isobutyl ketone	April 1980
Nitrobenzene	(October 1978)
O-Tolidine-based dyes	
Polychlorinated terphenyls	April 1979
Pyridine	April 1979
Quinone	
Toluene	(October 1978)
1,1,1-Trichloroethane	April 1979
Xylenes	(October 1978)

*Chemicals followed by dates in parentheses were designated by the Committee (Ref. 2) and responded to by the Administrator in 43 FR 50 134-50138.

TABLE 6-2. MONITORING SUPPORT PLANNED OUTPUTS

PROGRAM AREAS	FY-80	FY-81	FY-82	FY-83	FY-84
Methodology Development & Measurement System Research	Determine effectiveness of brake cleaning methods in limiting asbestos exposures. Determine effectiveness of dye tracers for detecting freon leaks from automobile air conditioners. Develop method for measuring PCB's in oil.	Publish method for routine analysis of aldicarb. Study the feasibility microbial systems for rapid detection of dioxin. Complete "production type" GC/FTIR system and protocol for analysis of dioxin in environmental samples.	Extend "production type GC/FTIR system to pollutants specified by OPTS. Publish methods for measuring OPTS specified organics in sediments. Publish streamlined method for multi-element analysis.	Publish method for measuring organics in marine systems. Study the feasibility microbial systems for rapid detection of organic compounds specified by OPTS.	Publish methods for measuring toxics in products specified by OPTS. Publish methods for OTS specified organics in sediments. Publish method for use of microbial system for rapid detection of pollutants specified by OPTS.
Field Collection Methodology and Monitoring Activities	Publish field methods for three specific chromophoric compounds including benzidene (air measurements). Publish field methods for separation and analysis of polar and hydrophilic compounds (air measurements).	Publish field methods for screening toxic air pollutants specified by OPTS. Collect monitoring data at sites selected by OPTS for assessment studies.	Publish protocol on multi-media field procedures to validate a stream model. Collect monitoring data at sites selected by OPTS for assessment studies.	Publish field methods for screening toxic air pollutants specified by OPTS. Collect monitoring data at sites selected by OPTS for assessment studies.	Publish protocol on multi-media field procedures to validate model selected by OPTS. Collect monitoring data sites selected by OPTS for assessment studies.
Quality Assurance	Publish good laboratory practices guidelines for transport and fate and environmental processes. Publish quality assurance protocol for measuring asbestos in ceilings.	Implement mandatory quality assurance program.	Develop guidelines and protocols as required.	Develop guidelines and protocols as required.	Develop guidelines and protocols as required.

TABLE 6-3. METHODOLOGY DEVELOPMENT AND MEASUREMENT SYSTEM RESEARCH

RESEARCH	PROGRAM AREAS	FY-80 PROJECTS	RESOURCES	
			FY-80	FY-81
	Air	Develop HPLC detector characterization methods using GCMS/HPLC optimization of methods for collecting PCBs.	$351,000	$618,000
	Water	Maintain access to Mass Spectrometry Search (MSS) library.	50,000	
CHEMICAL	Soil/Sediments	Refine separation, characterization and quantification methods.	129,000	
	Efficiency Improvements	Refine multiple GC, FTIR, interface routine multi-element analysis techniques.	70,000	100,000
BIOLOGICAL	Characterization in marine animals and plants			-0-
	Biological Monitors	Develop screening methods for dioxin.	80,000	200,000

TABLE 6-4. FIELD METHODS AND MONITORING SUPPORT

PROGRAM GOAL	PROGRAM AREAS	PROGRAM FY-80	RESOURCES	
			FY-80	FY-81
	Air	Fenceline Monitoring Methods/Benzidene Focus	$ 480,000	$ 504.00
Methodology Development and Model Validation	Multi-Media	Stream Model Validation Study	865,000	949,000
		Exposure Assessment Methods	-0-	1,011,000
	Public Health	Integrated Assessment Field	-*	
		TOTAL	$1,345,000	$2,464,000

*Funded in environmental program

TABLE 6-5. CHEMICAL SPECIFIC RESEARCH

1980 PROGRAM AREAS		RESOURCES FY-80
PCBs in Oil		$40,000
Freon/Asbestos in Cars		$50,000
	TOTAL	$90,000

SECTION 7

ENVIRONMENTAL ENGINEERING AND TECHNOLOGY RESEARCH STRATEGY

The subcommittee for Environmental Engineering and Technology was recently established to plan the research and provide experience and expertise in subjects relevant to OPTS program activities. The subcommittee is co-chaired by Mr. Carl Schafer (ORD) and Dr. Roger Garrett (OPTS).

I. OVERVIEW

OPTS actions under Sections 5 and 6 of TSCA require support in the assessment of potential risks involved in the manufacture, use, and ultimate disposal of new and existing chemical products. Engineering analysis provides the basis for assessing human and environmental exposures to products of concern by identifying the modes, physical form, extent, and points of generation and release of harmful or potentially harmful substances to the environment within the product life cycle. Environmental assessment (including consideration of health and ecological exposure impacts) of such substances will only be as valid as the engineering analysis. This analysis is therefore central to the support of a sound toxics research and assessment program.

II. BACKGROUND AND STATUS

The establishment of the Environmental Engineering and Technology Research subcommittee creates the impetus for a significant shift in researh emphasis. For three years the environmental engineering program element in the toxics research and development decision unit has centered on support evaluation of PMN and engineering analysis of certain hazardous activities (i.e. asbestos removal, PCB's destruction, etc.). This past effort is characterized as short-term technical support rather than as research. Formation of the new research subcommittee will enable ORD to conduct long-term research to establish a knowledge base for engineering analysis of a wide spectrum of environmental concerns. In addition, it will broaden the ORD capability to support OPTS in assessing the risks of a multiplicity of toxic substances.

III. RESEARCH GOALS

The Environmental Engineering and Technology subcommittee has four overall goals.

- To provide specialized technical assistance to resolve complex problems.
- To develop research capabilities to meet long-term implementation time frames.
- To develop a comprehensive long-range program to refine continually assessment schemes.
- To build continuity and stability into the program to meet future challenges.

ORD will support EPA's toxic substances program by providing the expertise and methodology for toxic hazard and exposure assessment.

OPTS will require improved hazard assessment test evaluation procedures, both to analyze data from industrial sources and to support its own results for regulatory purposes. Enhanced exposure assessment methodology will provide additional depth to the program by allowing EPA toeva;iate better exposure levels of a variety of harmful and potentially harmful substances and the potential risks they pose to humans and the environment. Exposure parameters to be documented include toxic chemical generation, use, distribution, and disposal.

ORD will continue to aid OPTS with short-term projects not necessarily covered under TSCA. Chemicals of specific regulatory and research interest will be studied. Pilot efforts to initiate a long-range research program will be carried out to build the framework for the new subcommittee's planning. Thus, ORD's research program will effectively converge with EPA's effort within OPTS to implement TSCA with respect to the study, evaluation, and documentation of the health and environmental impacts of toxic substances.

The program will be designed to support OPTS efforts by:

- Determining the occurence of selected toxic substances through engineering analysis of their sources in the products
- Recommending alternative manufacturing process options for the processing and/or production of potentially hazardous or toxic materials
- Providing technical expertise and specialized engineering for toxics regulatory actions

FY 80 research activities supporting TSCA will be redirected, to the extent possible, to establish toxics program elements for future long-term research.

IV. RESEARCH APPROACH

EPA will continue to carry out systematic assessments to identify the toxic product contaminants and pollutants discharged to air, water, and land by the chemical inustry. This work originally focused on product-specific commercial processes, such as those to produce aniline, alkyl amines, and acrylonitrile. However, emphasis has been recently shifted to achieve broader industry coverage by focusing on the toxic discharges and product contaminants from generic processes. Toxic discharges for allied chemical process industries including pesticides, pharmaceuticals, food activities, petroleum refining, textile fibers, and dyes and inks will be assessed. The outputs from these assessments will be managed through the establishment of an engineering analysis data base, a knowledge resource which will receive increased use by the toxics regulatory offices of the Agency. Recently, the Organic Chemical Producers Data Base (OCPDB) has been expanded to include information on potential risks involved in the production and use of some 600 organic chemicals. Further OCPDB expansion will include data on the various satellite industries such as plastics, dyes and pigments, and pharmaceuticals. Data on the exposure potential inherent in various chemicals or chemical processes will be developed. These data will be of particular value to OPTS in assessing the potential risk involved in a new or existing chemical's manufacture and use.

Through in-process evaluations of specific manufacturing processes, the toxic chemical(s) inadvertently generated and introduced into products will be identified. Such evaluations can also pinpoint those in-process toxics sources that will require regulation under TSCA and other applicable statutes. Over the next five years, ORD will focus on developing alternative manufacturing methods and process conditions to reduce the occurrence of toxic product contaminants. Additionally, ORD will evaluate the possibility of developing substitutes for chemicals that pose toxic threats.

This broadened approach to toxics engineering analysis will greatly expand OPTS's potential for regulatory action under TSCA.

ORD thus anticipates the imposition of new, more rigorous regulations for the reduction of toxic effluents from operations producing major organic chemicals. Projected economic impacts of these regulations have been based on the premise that capital and operating costs of newly required control or modified facilities will be added to the price of the materials produced and passed on to the ultimate consumers.

However, in reality, plant owners have a number of alternative responses to the imposition of new effluent control requirements. Their choices will be dictated by their preception of their best business judgment as well as the analysis of the data available to them. In this respect, these decisions can be made exactly as other business decisions unrelated to environmental concerns.

In order to assess the most probable economic impacts of the introduction of any particular regulation, the toxics program must anticipate the nature of industry decisions. Effects on employment import levels, and cost to the U.S. economy, in fact any change imposed by industry actions, must be estimated.

The various options open to chemical industry management will in many cases interact with one another. There will usually be secondary and tertiary effects of any decision. Optimum strategies will vary from company to company, and often from plant to plant, because of their specific circumstances or philosophies. Thus the overall industry response to any requirement will often be a mixture of several strategies. The questions that industry should consider are:

- Shifts In Feedstocks: What possibilities are there to to shift to a more expensive feedstock to eliminate formation of noxious effluents? At what cost would this be economical?
- Alternate Processes: Are there alternate processes that could produce the same product without producing the prescribed effluent? What are the relative economics of the alternatives?

This research program effort directed at predicting industry response to regulations will enable OPTS to develop realistic toxics regulatory strategies and to promulgate regulations that will effect realization of OPTS legislative objectives.

APPENDIX

TABLE A-1. FUNDING FOR THE PROGRAMS COVERED IN THE CHEMICAL TESTING & ASSESSMENT RESEARCH STRATEGY - AUGUST, 1980

Program	FY 1979[1] ($000)	FY 1980[2] ($000)	FY 1981[3] ($000)	FY 1982[4] ($000)	FY 1983 ($000)	FY 1984 ($000)	FY 1985 ($000)
Health Effects	$ 6,609.6	$ 9,252.4	$12,798.3	$14,078.1	$15,485.9	$17,034.5	$18,737.9
NCTR[5]	4,500.0	4,500.0	4,500.0	4,500.0	4,500.0	4,500.0	4,500.0
Environmental Processes and Effects	4,798.3	11,515.7	15,730.9	17,304.0	19,034.4	20,937.8	23,031.5
Monitoring Systems and Quality Assurance	2,977.8	3,510.7	3,782.0	4,160.2	4,576.2	5,033.8	5,537.2
Environmental Engineering and Technology	459.9	1,636.1	1,771.7	1,948.9	2,143.8	2,358.2	2,594.0
Stratospheric Modification	1,141.1	1,401.0	1,412.1	1,553.3	1,708.6	1,879.4	2,067.3
Total	$20,486.7	$31,815.9	$39,995.0	$43,544.5	$47,448.9	$51,743.9	$56,467.9

[1] FY 79 Actual Expenditures

[2] FY 80 Operating Plan

[3] FY 81 Request to Congress

[4] Funds for FY 82-85 are projected at 10% per year. This is the percentage used for the "moderate growth scenario" in ORD's Research Outlook, an annual report to Congress.

[5] NCTR--National Center for Toxicologic Research. Funds shown are EPA's annual support to NCTR through agreement with the Food and Drug Administration.